THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 80 NOVEMBER, 1958 No. 5

RADIOACTIVITY AND THE HUMAN SKELETON*

JANEWAY LECTURE, 1958

By L. D. MARINELLI
Radiological Physics Division, Argonne National Laboratory
LEMONT, ILLINOIS

IT IS with a profound sense of responsibility that I stand here tonight to address this learned society in honor of Dr. Henry Harrington Janeway. As a physicist, I cannot adequately comment upon his outstanding and pioneering contributions to surgery and radium therapy; nor can I recall episodes arising from personal contact, for I came to this country several years after his death. As a radiological physicist, however, I consider myself directly in his debt because I am, in a sense, a product of the very physics laboratory which he was influential in establishing at Memorial Hospital in 1916 under the leadership of Dr. G. Failla. I am, therefore, all the more conscious of the great honor conferred upon me and I wish to convey my deepest gratitude to the Janeway Lecture Committee for including me in a roster of illustrious speakers.

This lecture concerns radioactivity in the human skeleton and its most feared effect; namely, the production of cancer in bone.

Initially and for more than two decades, this subject enlisted the attention of a limited but devoted number of clinical and experimental investigators interested in the toxicology of radium. With the discovery of nuclear fission and its applications to war and peace, this topic has rapidly attracted the interest of an increasingly larger group of people; with the world-wide appearance of strontium 90 in the fallout of nuclear detonations, it has become a matter of universal concern and widespread debate.

Simultaneously with these developments, new groups of assiduous workers have been accumulating useful data bearing on the toxicity of bone seekers in laboratory animals and are continuing their tasks with undiminished industry and enthusiasm. Much has been learned from their efforts, but since the relentless demand for information has outrun the supply, the fervor and the extent of the discussion have persisted unabated.

It is my wish this evening to outline a few salient points of what has been done and what remains to be done in the direct appraisal of the cancerogenesis to be expected from the deposition of radium in the

* The Twenty-third Janeway Lecture delivered at the Fortieth Annual Meeting of the American Radium Society, Hollywood, Florida, March 27–29, 1958.

Work performed under the auspices of the United States Atomic Energy Commission.

human skeleton; for it is in this approach that I see the best chance of evaluating in the foreseeable future what are the delayed effects of persistent low concentrations of any type of radioactive material in the human skeleton.

It should be recalled that, historically, the first maximum permissible level to be established was the limit of 0.1 μg. of Ra in the human skeleton and that it was meant to apply to an industry employing a few thousand people.[22] This level was established in 1940 on the basis of late (seven to twenty years) effects noted in radium dial painters in the state of New Jersey; it was chosen by taking one-tenth the lowest body burden observed to be present in seriously injured workers and thus included an "engineering safety factor" of 10.

The matter rested there until more than ten years later, when it became necessary to recommend occupational limits of contamination in water and in air.[21] From the assumption that 1.5 per cent of any Ra ingested reached the skeleton and that it remained there with a half life of 1.6×10^4 days, it was calculated that lifetime drinking of water with Ra content of 40 μμc /liter would not result in a skeletal accumulation greater than 0.1 μc. It was also thought, shortly afterwards, that in the interest of caution, both skeletal burden and water content should be reduced by another factor of 10, or possibly of 100, when large populations were involved.

These reductions would have meant concentrations (4 and 0.4 μμc/liter of water) much lower than those reported for the drinking water supplies of Frankfurt in Germany[16] and of Pittsburgh, Pennsylvania.[4] At the time there was no reason to doubt these reports because published analysis of human bones from the vicinity of Frankfurt[16] indicated that the radium skeletal burden of unexposed individuals could be as high as 0.01 μc. Since no obvious bone damage in the population of these two relatively large cities was known to exist, immediate confirmation of these values was sought concurrently at the University of Rochester and at our Laboratory. It was soon found that the true concentrations were lower by more than two orders of magnitude.[10,11,37] At the same time, however, it was found that some Illinois communities, comprising a total of 10^5 persons in the vicinity of Chicago, had been drinking for half a century waters containing Ra in amounts close to or exceeding the highest of the proposed limits for the general population and that these waters contained comparable amounts of Ra^{228}, which also deposits in the skeleton and adds to the α activity of bone.[37,39]

It became increasingly clear that more systematic hydrological studies were necessary; the challenge was taken up by several laboratories, including our own. Thus far, two extensive studies have been reported. One, by Dr. Hursh at the University of Rochester, covers the water supplies of 41 cities of the country comprising one-fifth of the population of the United States.[10,11] His findings are representative of surface waters utilized by large cities and indicate an average value of only 0.04 μμc/liter of water. The other, covering the drinking water of many smaller towns in about one-half of the counties of the State of Illinois, has been completed by Lucas and Ilcewicz[18] and Stehney[37] of our laboratory with very interesting results, some of which, concerning values more than 100 times those found by Hursh, are shown in Table 1. These findings can be summarized by stating that, thus far, about 9 per cent of the State population, excluding the City of Chicago, has been found to drink water containing radium isotopes in quantities greater than the maximum permissible Ra^{226} level adopted for large populations.

In order to ascertain to what extent differences in radium content of water of this order of magnitude affect the radium content of the skeleton, it becomes necessary to investigate the relationship between the *total* radium intake and the amount of radium in the skeleton. The other source of radium intake to be considered is food, since the intake of radium through inhala-

TABLE I

CONCENTRATION OF Ra^{226} IN DEEP SANDSTONE WELLS
(Lucas and Ilcewicz,[18] ANL-5829, January 1958)

Municipality	μμc/l.	Population	Municipality	μμc/l.	Population
Aledo	3.6	2,920	Lockport	8.0	4,950
Aurora	5.0	49,000	Minonk	8.0	1,950
Byron	4.6	1,240	Morris	6.3	6,930
Chenoa	4.3	1,450	Oregon	3.5	3,200
Cuba	11.0	1,480	Ottawa	6.6	16,000
Elmhurst	4.3	18,000	Plainfield	8.2	1,760
Farmington	7.5	2,650	Rockford	3.6	88,000
Freeport	3.6	23,000	Shannon	17.3	670
Granville	10.2	980	Sterling	4.8	12,000
Ipava	25.4	670	Toluca	7.4	1,420
Joliet	5.0	46,000	Wyoming	11.1	1,500
Lemont	8.0	2,700			

tion of air is too small by comparison. Not many data are available; Table II shows the results of Shandley,[36] who on the basis of the dietary habits of the United States population concluded that the average intake of radium through food was of the order of 1 μμc per day. This value is consistent with the figure of 1.6 μμc resulting from the analysis performed by Stehney and Lucas[38] on excreta of residents of Chicago where the radium contribution of the water supply is negligible. Results in Germany,[20] also shown in the table, are a few times higher, but of the same order of magnitude.

It is now necessary to ascertain what amount of radium is actually accumulated in man as a function of his intake. Information on this point has been forthcoming through sampling of skeletons in the Eastern and Pacific Northwest sections of the United States by Hursh and Gates,[12] and Palmer and Queen,[24] respectively. Moreover, through the efforts of Stehney and Lucas[38] at the Argonne National Laboratory—consisting of very careful measurements of radon exhaled by normal people living in Chicago, where the radium content of water is very low, and in communities nearby, where this content is rather high—it is possible to distinguish the skeletal deposition due to food from the amount due to water. Needless to say, the data are actually representative of about 100 individuals, but they seem to be consistent in their implications. The results are summarized in Figure 1 wherein the skeletal Ra content is plotted versus the Ra water content; the skeletal burden of 0.3 to 0.5 $\times 10^{-10}$ g. at less than 0.1 μμc/l. of water indicates how much radium one should expect to find in an average skeleton in the United States as a result of Ra taken only through ordinary foods. Recent reports from Germany[20,26] and England[42] indicate that this figure may be somewhat higher there, presumably because of higher radium content in the food. A report in press[43] covering a wider sample of bones in the United States and elsewhere is in substan-

TABLE II

Ra CONTENTS OF FOODS

(Shandley,[36] UR-255, 1953)		(Muth, *et al.*,[20] 1957)	
Food	μμc/kg.	Food	μμc/kg.
Eastern Milk	.13	Milk	3.75
Midwestern Milk	.24	Wheat	2.6
Raw Haddock	.74	Wheat	2.0
Lima Beans	1.05	Potatoes	6.7
Kidney Beans	.8	Potatoes	12.5
Green Peas	1.9	Beef	.8
Pearled Barley	3.9		
Beef	0.0		

Average food intake 1–2 μμc day^{-1}.

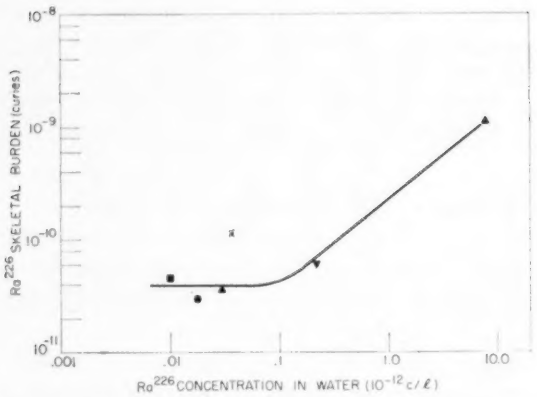

FIG. 1. Skeletal burden to be expected in adult populations drinking 2.5 liters of water per day: ×, Hursh and Gates;[12] ■, Palmer and Queen;[24] ●, Walton *et al.*,[43] ▲, Stehney and Lucas, corrected for water intake of 2.5 liters per day;[38] ▼, Rajewski *et al.*[26]

tial agreement with the above estimates for this country.*

It is possible from a graph of this type to predict with some confidence the average skeletal content of a population from the Ra concentration in its water supply, though it must be recognized that wide bone samplings pertinent to this question are highly desirable.

The justification of the .01 μg. Ra limit in large populations, however, remains untouched by these findings, since the limit (with no direct evidence to support it) is based entirely on an arbitrary factor of 100 from the burden at which definite evidence of damage was found prior to 1941. To assure ourselves on this point it is necessary to inquire into the relative incidence of bone cancer in communities where Ra skeletal burdens differ by substantial amounts.

At the present time Dr. H. Auerbach of the Division of Biological and Medical Research at the Argonne National Laboratory is working on detailed analysis of the average mortality by bone cancer in the State of Illinois during the eleven years ending in 1950. The study is not complete; some relevant data available at the moment are shown in Table III. These figures are preliminary and are presented principally with the intent of examining what must be done in order to obtain significant results. Before proceeding further, it should be realized that the human skeleton is subject also to other radiations, mainly from the radioactivity of the surroundings, cosmic radiation and the diagnostic use of roentgen rays. Possible variations due to these sources are neglected for the moment by assuming that they are constant in the populations of Illinois. The justification of these assumptions will require, by itself, an effort of no mean proportions.

From the estimated skeletal contents we can proceed to compare the bone cancer mortality rate in Chicago, with a skeletal burden of 0.4×10^{-10} g. of Ra, and the communities of Joliet, Aurora and Elmhurst with a value larger by a factor of about 15. It will be noted that the most apparent deficiency is the limited number of cases involved in the latter group in the eleven year survey. We find that the combined male and female rate is 2.17 in the suburbs as against 1.78 in Chicago—just outside the Standard Deviation of about 20 per cent. If we examine the male population, we have 1.77 as against 1.97—distinctly lower but within the standard error. On the other hand, the incidence in females; namely, 2.57 as against 1.59 in the two populations differs by more than two standard deviations. This finding is anomalous in that the female-male incidence rate (1.45) is reversed compared to the State (0.85) or the nation (0.685) as a whole. No ready explanation can be given since the experimental evidence available[12,20,23,24] shows comparable retention in the skeleton of both sexes and no special radiosensitivity of the female skeleton has been observed. Moreover, this anomalous ratio obtains also at Elgin where the combined incidence is also high, though the Ra concentration in the water is much lower.[37] Although the

* Incidentally, these data are consistent with the implications of the experimental findings of Norris *et al.*[23] who studied the pattern of retention in a group of patients injected with known quantities of radium in 1930. The German data[20,28] suggest relatively high contents in soft tissues, in sharp contrast to the accepted notion that most of the radium is in the skeleton.[34] This point needs further elucidation.

TABLE III

Location	Water Concentration $\mu\mu c/l.$	Bone Cancer Incidence*			Ra^{226} Burden 10^{-10} c	Population†
		Male	Female	Combined		
United States	~0.04	—	—	1.64	0.5 (?)	1.4×10^8
Illinois‡	>0.4	1.91	1.62	1.78	>1.1	4.8×10^6
Chicago	0.03	1.97	1.59	1.78	0.4	3.5×10^6
Elgin	0.7	3.19	5.01	—	1.8	4.1×10^4
(a) Joliet	5.0	.78	2.75	—	7.0	4.6×10^4
(b) Aurora	5.0	1.87	2.24	—	7.0	4.9×10^4
(c) Elmhurst	4.3	4.06	3.05	—	6.5	1.8×10^4
(a)+(b)+(c)		1.77	2.57	2.17	7.0	1.1×10^5

* 1940–1950—average bone cancer mortality per 10^5 population (jaw cancer excluded).
† 1940–1950—average.
‡ Illinois State (exclusive of Chicago).

industrial history of the towns in question, the presence of trace elements in the water such as fluorine, age adjustment, etc., are suspected causes, one may conclude temporarily that the figures at hand indicate that an increase from 0.4 to about 7.0 $\times10^{-10}$ g. Ra^{226} in the skeleton is unlikely to increase the combined incidence rate by more than 20 per cent; this is just about equal to the uncertainty to be expected from the 27 cases of bone cancer uncovered by the survey. It is hoped that bone cancer statistics pertinent to the remaining population ($2–3\times10^5$ individuals) at risk with comparable levels will help to clarify the situation.

Some indirect evidence that the latter group as a whole cannot contribute inordinately to the bone cancer rate of the State as compared to Chicago, can be gathered from the fact that if it were much more than 20 per cent, the State (Chicago excluded) should show a cancer incidence much greater than 20 per cent $\times0.1=2$ per cent over Chicago. The available evidence indicates identical rates with a statistical uncertainty of about 5 per cent (Table III). We may utilize these data more fully by noting that in addition to these natural regions of relatively higher skeletal content, there exists in the state a group of several hundred former dial painters whose burden, according to Dr. C. E. Miller's preliminary sampling of about 50, averages a few tenths of a microcurie.* We estimate that, with the inclusion of this group, the average body burden in Illinois is greater than 1.1×10^{-10} g., or about three times that of the Chicagoans. We may infer then that this difference in skeletal content is not likely to increase the incidence by more than the statistical uncertainty of 5 per cent. The data also suggest that the female-male incidence ratio in the State is not grossly anomalous since it is wholly comparable to that of Chicago (0.81).

At this point I should like to summarize by saying that, in essence, any increase in bone cancer that may exist at these levels is masked by statistical uncertainty. The latter can be materially reduced by covering more thoroughly other relevant populations both in the United States and abroad. The task constitutes a painstaking, but not impossible, undertaking. Already, from what has been learned about the extent of relevant acquifers in Illinois, there seems to be a fair probability of locating populations of interest in Iowa, Missouri and Wisconsin totalling from 1.5 to 2.5 million. To inspire confidence, these hydrological studies must be supplemented by appropriate dosimetric studies covering both internal and external radiation, by age adjustments and studies of the possible influence of other factors, such as mineral

* The possibility of the existence of a similar group in the city of Chicago remains to be explored.

contents of water, etc., and, most important of all, by refinements and improvements in death certification.

In order to extend the analysis to higher burdens, we turn to a group of individuals whose skeletons have contained for twenty to thirty years from 0.1 to 10 μc of Ra, namely, from thousand to hundred thousand times what we regard average normal burdens in the average citizen in the United States. This burden was acquired mostly by women between sixteen and twenty-five years, during periods of employment ranging from a few months to several years and by patients of various ages given Ra for therapeutic purposes. Because of this and other reasons, relating to inconstancy of dose rate and to uneven skeletal distribution, this group is not strictly comparable to the large populations that we have just considered, in which the dose to the skeleton is essentially uniform throughout the bone and constant in time.[43] The cancerogenic influence of these dosimetric factors cannot be evaluated with the knowledge available to us at the present time. They are known to act partly in opposite directions, and for the purposes of these approximate estimates, they can be disregarded without impairing some of our conclusions.

We shall recall only that, owing to the long term excretion of Ra^{226}, the cumulative average dose to the skeletons of these groups is roughly twice that which would accrue on the assumption that the burden found twenty-five years later had been constant back to the time of intake.[5] Hence, in comparing the two groups, the burden of the latter should be doubled.

It is well to summarize briefly what is known and what remains to be done at these higher levels. According to a very recent literature survey, 190 cases of radium poisoning have been reported. Unfortunately, reliable estimates of burden have been reported in less than one half of them. The Boston group, consisting of 30 patients and dial painters, was a group highly selected on the basis of symptoms.[2] The tumor incidence was 27 per cent in an average observational age interval of thirty to fifty-five years, corresponding roughly to 1,200 times the natural incidence in Chicago; the Ra content averaged 5.4 μc. The patients studied in Chicago[21] were a less selected group and the group at Elgin State Hospital[17] was entirely unselected. The incidences observed are 840 and 310 times Chicago's, respectively, with average burdens corresponding to 2.6 and 1.5 μc. True incidence at these levels, however, awaits some reliable estimate of the total number of individuals at risk and the burden distribution function of those exposed who have not come to the attention of the medical profession. If our experience in Illinois is any criterion of the situation at large, we must really confess that the prospects of tracing unselected therapeutic cases are rather dim and that the underlying reasons are beyond the control of the most discrete and most conscientious investigator. The prospects of tracing industrial cases are much brighter, thanks in great measure to civic minded executives of industry and local members of the medical profession who have given and still give unstintingly of their time and efforts. Current investigators in various sections of this country already have traced over 500 persons and there is every reason to believe that this number can be substantially increased by studies abroad.

Some use can be made of the preliminary data available concerning this group to take more than a hypothetical guess at the probable incidence of bone cancer in the neighborhood of occupational maximum permissible levels. To weigh matters on the conservative side, we recall that no case of bone cancer or clinically recognizable pathology due to Ra^{226}, or a combination of Ra^{226} and Ra^{228}, has been reported in individuals carrying burdens less than 0.4 μc. The number of people exposed to radium carrying burdens below this amount and which has been actually measured and reported in the literature[2,17] is dismally small: a total of 19, in fact, of which only

Table IV

Group Designation	Skeletal Dose*				Population	Bone Cancer Incidence†	
	Ra^{226}	Ra^{228}	Background Radiation	Total		Male	Female
Boston	5.4	?	8×10^{-4}	10.8	30		1,200
Chicago	2.6	?	8×10^{-4}	5.2	19		840
Elgin State Hospital	1.5	None	8×10^{-4}	3.0	19		310
Dial Painters	0.13	?	8×10^{-4}	.26	10^3		3.9
Chicago Suburbs	7×10^{-4}	7×10^{-4}	8×10^{-4}	2.2×10^{-3}	10^5	.90	1.62
Illinois	1.1×10^{-4}	1.1×10^{-4}	8×10^{-4}	1.0×10^{-3}	4×10^6	.97	1.02
Chicago	4×10^{-5}	4×10^{-5}	8×10^{-4}	9×10^{-4}	3.5×10^6	1.0	1.0
Thorotrast	4×10^{-5}	10^{-1}	8×10^{-4}	10^{-1}	10^3–10^4	?	?
Travancore	4×10^{-5}	10^{-1}	8×10^{-3}	8×10^{-3}	10^5	?	?

* Skeletal dose expressed in units equivalent to 1 μc of Ra^{226}+0.3 μc daughters permanently fixed in the skeleton. Background radiation estimated at 100 mrem per year. 10^{-10} μc Ra^{226} equivalent = 12 mrem/year.

† Chicago city 1940–1950 average = 1.0 (See Table III).

7 were dial painters. It is, however, known that in New Jersey alone, 800 persons were estimated to be in the dial painting industry[19] of which 242 were actually surveyed by the United States Public Health Service in 1933.[3,14,31,32] If we add to these the people traced recently in other states, we must conclude that the population in question is at least 10^3. We may ask ourselves what must be the true incidence of bone cancer that would have 50 per cent probability of showing no occurrence in a thousand women initially twenty-five years old, during a period of observation of twenty-five years. This probability can be calculated to be 6.6×10^{-4} or 3.9 times the cumulative incidence of the unexposed Chicago population of the same sex and average age observed for a comparable period of time.

In order to arrive at a realistic average burden for this group we have considered the 7 cases (0.02–0.4 μc) published in the literature[17] and an additional cancer-free group of 50 people recently measured in our laboratory.* If consideration is given only to the subjects with less than 0.4 μc and at risk for more than twenty-five years, we obtain a preliminary average of 0.13 μc. In the interest of conservatism we shall disregard the possible presence of Ra^{228} and consider this figure as the significant burden.

In the figures shown in Table IV, where we have listed the tentative results just discussed, the first four concern the high level patients as well as the above estimate made on the dial painter group as a whole, the last three pertain to the general population studies. Before proceeding further it is well to recall that in the latter case account should be taken of the presence of Ra^{228}. The few experimental data available[39,42] and theoretical deductions[6,27] agree on roughly setting the burden of Ra^{228} as dosimetrically equivalent to that of Ra^{226}; hence, the natural levels are twice the ones discussed previously.

In addition, two other groups appear to be worthy of investigation and are included in the table. The first consists of patients who were injected with thorotrast for diagnostic purposes many years ago. Histories of the order of fifteen years and more have been reported in the literature, but a precise breakdown is not immediately available. Endeavors in this direction have been started with the cooperation of Drs. R. Chamberlain and S. Thomas. If the 250 patients reported under observation in Den-

* It is worthy of note that the burden distribution in the latter is roughly similar to that published by the United States Public Health Service in 1933.[14]

mark[15] were to be extrapolated to the Western World in terms of population alone, this number could be as high as 25,000.* This may be a maximum, however, because the true number critically depends on the relative frequency of use of thorotrast in the different countries. I have included in the table the limits 1,000–10,000. Such patients, on the basis of recent studies carried out in various laboratories here and in England[13,27–30] should be carrying burdens of $MsTh_1$ (Ra^{228}) and daughters equivalent to burdens of around 0.1 μc of Ra; namely, burdens in the vicinity of the occupational permissible limit. This group should be regarded as an irreplaceable source of information and hence worthy of registry on a national and possibly on a global scale.

Within this population a smaller group is being considered: workers in thorium refineries which have been in existence for several decades. The information available up to now is practically nil, except for the result of an industrial hygiene survey according to which no overt incidence of disease was found.[1] We are planning to initiate exploratory studies in this direction in the near future.

Another group consists of fairly large populations in India and Brazil living over thorium-containing sands who are subject to continual external irradiation of the order of 1 r per year. This radiation dose, translated into equivalent burden, corresponds to .008 μc of Ra^{226}, if the relative biological effectiveness (RBE) of 4 is taken for α- as contrasted to γ-radiation, and if it is assumed that the skeletal contents are no more radioactive than elsewhere. This burden, which falls within the province of vital statistics, is about four times the average total rem burden estimated for our 4×10^5 Illinoisians. The population is estimated to be about 10^5; hence, statistically, it is at least as important. Let us hope that the competent authorities will have the possibility of inquiring into the bone cancer rate in addition to the genetic studies that have already been contemplated in these areas.[9]

Large populations living at high altitude may, on account of higher external dose due to cosmic radiation, contribute to our knowledge of the effects of external whole body irradiation on cancerogenesis in general, including bone cancer. Here, the task could be simplified by inquiry at a few populous centers such as Denver, Mexico City, Bogotá, Quito and La Paz, totalling several million people living at altitudes greater than 5,000 feet. The probability of success, however, is predicated on adequate measurements of average total background radiation,[33,35] including cosmic-ray neutrons, about which little has been done dosimetrically[25,41] and much less has been learned in an osteocancerogenic sense.

What has been discussed thus far can best be visualized by plotting the results which are given in Table IV in graphic form, as shown in Figure 2, wherein the ordinate indicates bone cancer incidence in man expressed as a multiple of the 1940–1950 Chicago average for the same age group and the same period of observation. The abscissa represents total bone radiation burden expressed in equivalent curies of Ra^{226} permanently fixed. This total burden includes Ra^{228} and an external dose-rate of 100 mrem per year equivalent to 8×10^{-10} curies of Ra^{226} permanently deposited in the skeleton. This method is chosen to provide a common scale for the various groups which have been considered. The solid line shown to the left refers to cancer incidence observed by Finkel[7,8] in mice injected with Sr^{90}. It is included merely to indicate the shape of the incidence curve as we know it to exist in a mammalian species, and it is drawn to coincide with the human data at high cancer incidence for ease of comparison. The resulting incidence curve—plotted to approach the computed point at 0.13 μc and to find its way among the statistical uncertainties of the normal populations of Illinois—looks altogether respectable, despite the limitations already mentioned. Its most enigmatic aspect concerns perhaps the shape that

* A single survey in the United States[40] traced over 4,000 cases, but patients-years at risk were not determined.

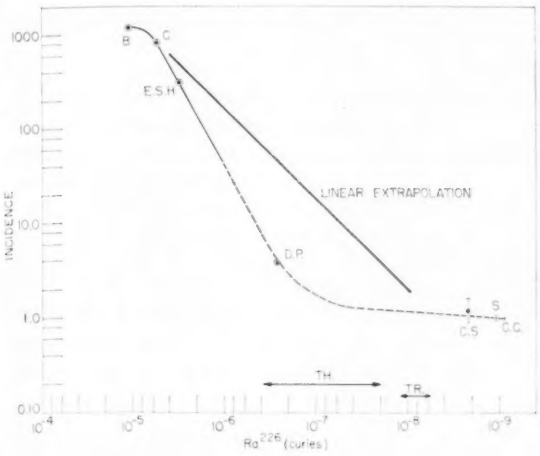

FIG. 2. Ordinate, bone cancer incidence in units of 1940–1950 average bone cancer mortality in Chicago. Abscissa, total radiation dose in terms of *constant* Ra^{226} burden. Points represent human data discussed in text: Patients from B(Boston), C(Chicago) and E.S.H. (Elgin State Hospital); Dial painters, D.P.; and General populations from C.S. (Chicago Suburbs), S (Illinois State) and C.C. (City of Chicago). Linear extrapolation is based on estimated incidence of 5×10^{-4} at 0.01 μc for the age period twenty to fifty years. Th: Dose range of thorotrast patients. TR: Equivalent burden of populations in Travancore.

it will assume at the higher burdens when these groups are followed to natural demise. Yet, from what is being learned about the time pattern of tumor appearance with dose fractionation of bone seekers in animals,[7,8] and from the radioactive content of those patients who have come to our attention since 1950, it seems unlikely that any point will be found in error by a large factor.

The curve, moreover, bears a striking resemblance in shape to the corresponding curve in mice. This is a detail that cannot be totally ignored by the proponents of the proportionality between dose and bone cancer incidence whose efforts are duly shown in the figure by a solid straight line. The validity of their or any other hypothetical extrapolation cannot be questioned on the basis of mechanism of bone cancer formation, since the latter is unknown. It cannot be effectively disputed, nor can the existence of a threshold invoked at low levels, because the results obtained, although highly suggestive of intangible damage, are subject to relatively large errors of various kinds. The strongest case against a linear extrapolation rests, for the moment, on the preceding arguments concerning the dial painter group with burdens near 0.13 μc of Ra. In this region, the discrepancy is too great to be attributed merely to errors in the conservative assumptions already stated. It is obvious, nevertheless, that the evidence at this level remains crucial from the practical standpoint and that the necessary tracing and follow-up* calls for all forces at our command. This work cannot be delayed much longer as these groups are disappearing because of advancing age and are becoming more difficult to locate because of dispersal throughout the country. For these same reasons a survey and follow-up of thorotrast patients takes on added significance. The size of both these groups can be increased substantially if other countries undertake similar studies. I sincerely hope that they will, since what is needed is the follow-up of cases with known exposure to radium or thorium, irrespective of the presence or absence of symptoms.

We may conclude that the problem confronting us can be solved if the tasks ahead are met with cooperative effort. Let us have the faith that this cooperation will be forthcoming spontaneously and/or under the sponsorship of some of the organizations which have been concerned heretofore almost exclusively with the prescription of norms of protection.

Let us also hope that, as the true magnitude of the task becomes more widely recognized, some of the current polemics on long-term effects of radiation will be carried out with greater humility, as demanded by the paucity of factual data.

Argonne National Laboratory
Box 299
Lemont, Illinois

* In the presence of a low cancer incidence due to radiation, a follow-up to natural death in a group of 1,000 women could improve considerably the uncertainty present in the above comparison between exposed and unexposed subjects, for the natural incidence increases sharply with age.

REFERENCES

1. ALBERT, R., KLEVIN, P., FRESCO, J., HARLEY, J., HARRIS, W., and EISENBUD, M. Industrial hygiene and medical survey of thorium refinery. *A.M.A. Arch. Indust. Health*, 1955, *11*, 234–242.
2. AUB, J. C., EVANS, R. D., HEMPLEMANN, L. H., and MARTLAND, H. S. Late effects of internally-deposited radioactive materials in man. *Medicine*, 1952, *31*, 221–329.
3. BLOOMFIELD, J. J., and KNOWLES, F. L. Health aspects of radium dial painting. II. Occupational environment. *J. Indust. Hyg. & Toxicol.*, 1933, *15*, 368–382.
4. BOTSET, H. G. Radium content of some connate waters. *Physics*, 1934, *5*, 276.
5. BRUES, A. M., and TYLER, S. Estimation of total radiation dose from radium. ANL-5518, 1956, 113–114.
6. DUDLEY, R. A., and EVANS, R. D. Radiation dose to man from natural sources. Proceedings of hearings of Joint Committee on Atomic Energy, 84th Congress, First session on the nature of radioactive fallout and its effects on man. Part 2, 1957, 1236–1246.
7. FINKEL, M. P. Induction of tumors with internally administered isotopes. To be published.
8. FINKEL, M. P., and SCRIBNER, G. M. Toxicity of strontium^{90} and calcium^{45} in mice. I. Status of experiments 625 days after injection. ANL-5597, 1956, 16–19.
9. GOPAL-AYENGER, E. R. Possible areas with sufficiently different background radiation levels to permit detection of differences in mutation rate of "marker" genes. In: Effect of Radiation on Human Heredity. World Health Organization monograph series, Geneva, 1957, 115–124.
10. HURSH, J. B. Natural occurrence of radium 226 in human subjects, in water and in food. (Measurement of Body Radioactivity.) *Brit. J. Radiol.*, 1957, Suppl. 7, 45–53.
11. HURSH, J. B. Radium content of public water supplies. UR-257, May 4, 1953.
12. HURSH, J. B., and GATES, A. A. Body radium content of individuals with no known occupational exposure. *Nucleonics*, 1950, *7*, No. 1, 46–59.
13. HURSH, J. B., STEADMAN, L. T., LOONEY, W. B., and COLODZIN, M. Excretion of thorium and thorium daughters after thorotrast administration. *Acta radiol.*, 1957, *47*, 481–498.
14. IVES, J. E., KNOWLES, F. L., and BRITTEN, R. H. Health aspects of radium dial painting. III. Measurements of radioactivity in workers. *J. Indust. Hyg. & Toxicol.*, 1933, *15*, 433–446.
15. JOHANSEN, C. Histological changes in man and rabbits after parenteral thorium administration. Radiobiology Symposium 1954, Bacq & Alexander Eds., Butterworths Scientific Publications, 1955, 358–360.
16. KREBS, A. Über die normale und anormale Radioaktivität menschlichen und tierischen Gewebes. *Fundamenta radiol.*, 1939, *5*, 89.
17. LOONEY, W. B., HASTERLIK, R. J., BRUES, A. M., and SKIRMONT, E. Clinical investigation of chronic effects of radium salts administered therapeutically (1915–1931). AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1955, *73*, 1006–1037.
18. LUCAS, H. F., JR., and ILCEWICZ, F. H. Natural radium 226 content of Illinois municipal waters. Radiological Physics Division, Semiannual Report, ANL-5829, 1958, 125–135.
19. MARTLAND, H. S. Occurrence of malignancy in radioactive persons. *Am. J. Cancer*, 1931, *15*, 2435–2516.
20. MUTH, H. *et al.* Measurements of normal radium burdens. (Measurement of Body Radioactivity.) *Brit. J. Radiol.*, 1957, Suppl. 7, 54–66.
21. National Bureau of Standards, Handbook H52. Maximum permissible amounts of radioisotopes in human body and maximum permissible concentrations in air and water. March, 1953.
22. National Bureau of Standards, Handbook H27. Safe handling of radioactive luminous compound. May 2, 1941.
23. NORRIS, W. P., SPECKMAN, T. W., and GUSTAFSON, P. F. Studies of metabolism of radium in man. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1955, *73*, 785–802.
24. PALMER, R. F., and QUEEN, F. B. Normal abundance of radium in cadavers from Pacific Northwest. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1958, *79*, 521–529.
25. PATTERSON, H. W., HESS, W. N., MOYER, B. J., and WALLACE, R. W. Flux and spectrum of cosmic-ray-produced neutrons as function of altitude. UCRL-8208, May, 1958.
26. RAJEWSKY, B., MUTH, H., HANTKE, H., and AURAND, K. Weiter Ergebnisse zur Frage des natürlichen Radiumgehaltes des menschlichen Körpers sowie von Nährung und Trinkwasser. *Strahlentherapie*, 1957, *104*, 157–168.
27. REYNOLDS, J. C. Calculation of retention and elimination of Ra^{228} and Ra^{224} from a single injection of Th^{232}. Radiological Physics Division, Semiannual Report, ANL-5829, 1958, 51–60.
28. REYNOLDS, J. C., GUSTAFSON, P. F., and MARINELLI, L. D. Retention and elimination of radium isotopes produced by decay of thorium parents within body—calculations and comparison with experimental findings. ANL-5689, October, 1957; also, Marinelli, L. D. Relevance of skeletal burden of thorotrast to problem of chronic toxicity of bone seekers in man. *Radiology*, 1957, *70*, 93–94.

29. Rotblat, J., and Ward, G. Radioactivity from thorotrast and its retention in tissues. *Phys. in Med. & Biol.*, 1956, *1*, 125–137.

30. Rundo, J. Radioactivity of thorotrast. *Phys. in Med. & Biol.*, 1956, *1*, 1–9.

31. Schwartz, L., Makepeace, F. C., and Dean, H. T. Health aspects of radium dial painting. IV. Medical and dental phases. *J. Indust. Hyg. & Toxicol.*, 1933, *15*, 447–455.

32. Schwartz, L., Knowles, F. L., Britten, R. H., and Thompson, L. R. Health aspects of radium dial painting. I. Scope and findings. *J. Indust. Hyg. & Toxicol.*, 1933, *15*, 362–367.

33. Sievert, R. M. Exposure of man to ionizing radiations, with special reference to possible genetic hazard, in: Effect of Radiation on Human Heredity. World Health Organization, monograph series, Geneva, 1957, 63–85.

34. Silberstein, H. E. Historical background. In: Biological Studies with Polonium, Radium and Plutonium. Robert M. Fink, Editor. N.N.E.S. VI-3. McGraw-Hill, New York, 1950.

35. Solon, L. R. Measurements of external environmental radiation in the United States. *Science*, 1958, *127*, 1183.

36. Shandley, P. D. Radium content of common foods. UR-255, April 22, 1953.

37. Stehney, A. F. Radium and thorium X in some potable waters. *Acta radiol.*, 1955, *43*, 43–51.

38. Stehney, A. F., and Lucas, H. F., Jr. Studies on radium content of humans arising from natural radium of their environment. Peaceful Uses of Atomic Energy: Proceedings International Conference, Geneva, August, 1955, New York. United Nations, 1956, *11*, 49–54.

39. Stehney, A. F., and Wallace, D. E. Th^{228}, Ra^{228}, and Ra^{226} in normal bone and in bone specimens from radium patients. Radiological Physics Division, Semiannual Report, ANL-5829, 1958, 115–120.

40. Thomas, S. F., Henry, G. W., and Kaplan, H. S. Hepatolienography: Past, present and future. *Radiology*, 1951, *57*, 669–684.

41. Tobias, C. A. Radiation hazards in high altitude aviation. *J. Aviation Med.*, 1952, *23*, 345–372.

42. Turner, R. C., Radley, J. M., and Mayneord, W. V. Alpha ray activities of humans and their environment. *Nature*, 1958, *181*, 518–521.

43. Walton, A., Kologrivov, R., and Kulp, J. L. Concentration and distribution of radium in normal human skeleton. To be published in *Health Physics*.

CANCER OF THE BREAST*

A STUDY OF SHORT SURVIVAL IN EARLY CASES AND OF LONG SURVIVAL IN ADVANCED CASES

By D. W. SMITHERS, M.D., F.R.C.P., F.F.R.
LONDON, ENGLAND

THE settled days when the Halsted radical mastectomy was widely accepted as the only effective treatment for cancer of the breast are past. In some centers the classic operation has been giving way to local mastectomy and radiation therapy; in others to still more radical surgery. Radiation therapy has become a regular part of treatment in some hospitals while still being regarded as of doubtful value elsewhere. Hormone therapy and endocrine gland surgery increase in importance, but despite dramatic tumor regression at times we remain uncertain of the precise indications for these treatments and have yet to reduce the disadvantages to the many so that we may be sure they do not weigh too heavily against the benefits to the few. Through all this therapeutic upheaval the results of treatment, in terms of survival rates in individual hospitals, have been improving all over the world, and yet the age-specific death-rates in large communities have remained constant. It is important that in trying to find our way through this new and healthy confusion we refresh our view of the problem by constant reference to the natural history of the disease and by a genuine attempt to evaluate all the available therapeutic measures, especially those we do not ourselves practice.

Within this setting I would like to discuss some trends in breast cancer mortality and in treatment results, with special reference to the unexpected and what we may learn from it. Much of the present material arose from a study of some patients with advanced disease who survived for many years and of others with early disease who died soon after treatment. My purpose in this inquiry was to try to find evidence to test the opposed theories that no treatment affected the predetermined pattern of human breast tumor behavior on the one hand, and that even more drastic treatment is required if we are to alter its course profoundly on the other. Since early breast cancer is regularly curable, since its inevitable, relentless progression has been called in question both by statisticians and by clinical observations, and since some patients may nevertheless die of this disease within a few months of its onset, our failures form a matter of particular interest. Since advanced breast cancer is still commonly seen, since its invasiveness and danger to life once it has reached this stage cannot well be denied and since it is at this point that hormone therapy must prove its worth, it also seemed to be of special interest for study at this time.

TRENDS IN BREAST CANCER MORTALITY

It is to be expected that the number of women dying of breast cancer will increase; there are more of them and they are living longer. In England and Wales in 1940 there were under 7,000 deaths registered as due to this cause in women; in 1950 there were 8,000 and in 1956 there were 8,580. The death-rates for each age group have not, however, been changing appreciably in recent years. In England and Wales, for example, the mean annual death-rate per million living at the ages forty-five to forty-nine in 1921–1925 was 455 and twenty-five years later, in 1946–1950, it was 452. The corresponding figures for the age group sixty-five to sixty-nine at these times were 927 and 1,000.[34] Unchanging age-specific death-rates have been noted in other countries over the past few decades[26] and this uniformity has been regarded by McKinnon[19] and others as evidence against the

* Presented at the Fifty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 1–4, 1957.

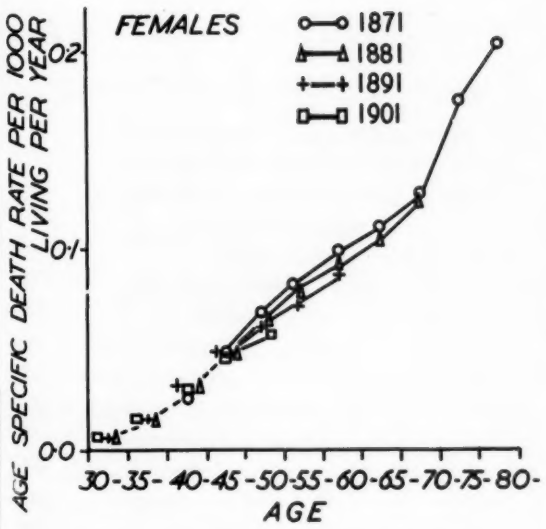

Fig. 1. Trend of age-specific mortality in breast cancer for nearly one hundred years (Case 1956).

efficacy of cancer education and control programs and, indeed, against the value of any present treatment method as a means of influencing the course of the disease. Although these death-rates have shown little variation within each country in recent years, they do show considerable differences in level from one country to another.[27] Stocks[34] examined the death-rates from 1921 to 1950 among women born from 1865 to 1910. He found that there had been a tendency for the rates to fall after the age of fifty, but to increase before the age of forty-five. This method of cohort analysis was applied to cancer in some detail by Case[3] who also showed that the chance of dying of cancer of the breast past the age of fifty had been getting steadily less for women born in each successive five-year period for nearly one-hundred years (Fig. 1).

It seems that the number of deaths from breast cancer has been increasing, that the death-rates in each year at each age have remained much the same, but that the chance of dying of breast cancer at any age past fifty has been getting steadily less for each generation. The chance of dying of breast cancer under the age of forty-five is still small, but this chance may possibly be becoming greater for each group of people born in successive years.

Some changes have been taking place over the last few generations which may have affected the incidence of this disease. The considerable variation from one country to another may reflect hereditary tendencies or be an indication of the possible fluctuations which may occur in incidence due to varying conditions of life. Perhaps the most important fluctuation in Britain has been the progressive fall in family size. The chance of a woman developing breast cancer is related to her number of pregnancies[32] so that the risk is considerably less among those who have had several children than among those who have had no more than one. Where the average number of children women have is falling, the incidence of breast cancer should be rising. Stocks[34] estimated that an increase of breast cancer in England and Wales of as much as 9 per cent after forty-five years of age might have been expected on this account in the past thirty years, and that since there had been no increase in death-rates a corresponding rise in survival-rates was likely.

No big change in death-rates in large populations due to improved treatment can be expected until such improvement is applied to more than a small fraction of the patients who develop the disease. The habit of recording death as due to cancer in any patient who has once been known to have the disease, even if treated successfully, tends to keep down any sign of improvement. There is no reason to deny the great body of clinical evidence in favor of the effective treatment of breast cancer solely on the broad, national statistical grounds proposed, nor any call for self-satisfaction over our treatment record until we have made an undoubted impression on the age-specific death-rates in large communities.

TRENDS IN TREATMENT RESULTS

When we compare the results obtained by treatment in individual hospitals, great

caution is required. Improvement may be due to a change in selection of patients attending the hospital, to a change in the malignancy of the tumors occurring, to a reduction of delay in starting treatment, to a relative improvement in the diagnosis of the less malignant tumors, to a better selection of the most suitable treatment or combination of treatments for each individual patient, or to an absolute improvement in the effectiveness of the treatment given. No hospital results should be accepted for comparison with others unless the total number of new patients with the disease seen in the period under review is presented, whether they were all treated or not, or whether they were treated at that center or sent elsewhere. If we are to attempt comparisons, no selection within the total experience of that hospital of that disease is permissible until the full results, accepting those lost sight of as dead, have first been presented.

In our own reporting we include all patients who have had any part of their first planned treatment at our hospital, even if they have had an operation elsewhere and have only come to us for postoperative irradiation because the disease has been found to be more extensive than was expected. We also include those seen by us before treatment who, because of advanced disease or personal wish, were treated nearer to their homes. These inclusions lower our survival-rate by selectively adding patients with a bad prognosis, often treated in a way we would not ourselves have advised. We endeavor to stop the practice of sending half-treated patients to out hospital instead of consulting about the treatment before it is started, but do not eliminate these patients from our records.

In 1952 we presented a review of results from different parts of the world, in hospitals where all patients seen had been recorded.[32] Figure 2 is a modification of that chart. It shows that the survival in patients seen with breast cancer in hospitals in many parts of the world has been steadily improving and may be approaching a 50 per cent five year rate. That the quality of

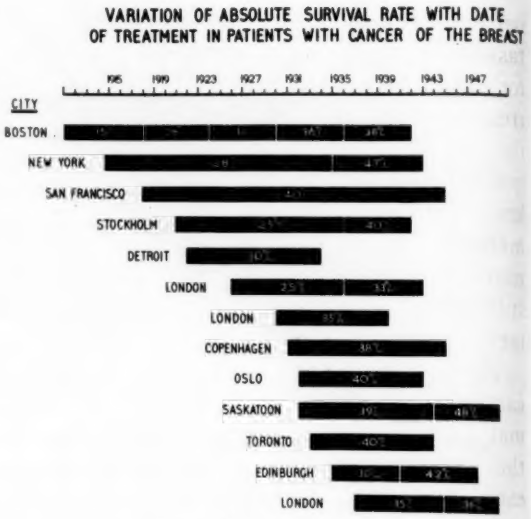

FIG. 2. Variation of absolute survival rate with date of treatment in patients with cancer of the breast as reported by different authors: Taylor[35] (Boston 1949); Haagensen and Stout,[10] and Haagensen[11] (New York 1942 and 1949); Shimkin *et al.*[30] (San Francisco 1952); Berven,[1] and Nohrman[24] (Stockholm 1949 and 1949); Evans and Leucutia[8] (Detroit 1939); Truscott,[36] and Windeyer[40] (London 1947 and 1949); Williams *et al.*[39] (London 1953); Kaae[15] (Copenhagen 1952); Engelstad[7] (Oslo 1948); Watson[38] (Saskatoon 1957); Richards[28] (Toronto 1948); McWhirter[20,22] (Edinburgh 1948 and 1955); and The Royal Marsden Hospital (1952 and 1957).

the material presenting for treatment is the prime reason for the better rates in most centers is almost certain. The lack of improvement in stage distribution in our own material is the chief reason for our comparatively steady survival-rate, which nevertheless shows considerable variation from year to year (Fig. 3). The result obtained in all patients seen at our special breast cancer clinic, who are either not treated or receive all their treatment at our hospital, is a good deal better. The success of the work of the Saskatchewan Cancer Commission in attracting patients earlier for treatment is a good example of what can be done and the improvement in survival which it can obtain is shown in Watson's[38] report. A center which is treating more patients in an early stage, seeing a larger proportion of the total cases occurring within its territory and achieving a

better survival-rate is performing a good task. It is improving the chance of recovery for patients in its area whether or not the treatment offered has itself improved or the survival-rate within each stage remained unchanged. It is, however, well known that an improvement in treatment methods has taken place. What is uncertain is how much improvement in results is still possible with any local treatment method, however efficient.

The chief therapeutic interest in breast cancer, at present, centers, first, in the optimal coordination of surgery and radiation therapy into the best treatment plan for each individual, which includes attempts to improve the means at our disposal for assessing in advance what this may be, and, second, in attempts to take a really big step forward by obtaining control of the disseminated disease through hormonal alterations.

SHORT SURVIVAL IN EARLY CASES

In early cases treatment by surgery and radiation therapy gives excellent results. So long as the disease is still well localized, cure follows in most cases. These treatment methods, however, fail altogether to deal with blood-stream dissemination.

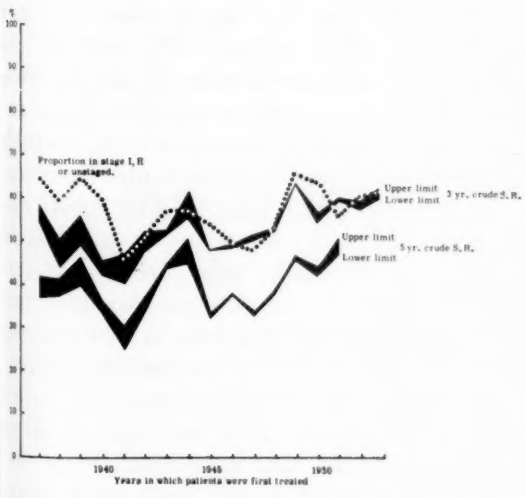

Fig. 3. New patients with cancer of the breast, 1937–1953. Crude survival rates at three and five years for patients treated in each year related to the proportion in the early stages (Royal Marsden Hospital). (Reproduced with permission.)

The results obtained in Stages I and II have lately been improving little in the best centers, probably because they have for some time been not so very far short of the best which local treatment methods can achieve. Results in the early stages following different treatment combinations also differ little, chiefly again because they are all equally ineffective in dealing with the main cause of failure, which is blood-borne metastases. Extensive operations for early localized growths in the breast are unnecessary and, if they produce much disability, quite inexcusable; for patients who already have dissemination by the blood stream they offer mutilation without hope. If they have a place in the treatment of breast cancer, it is in that small group of patients with extensive lymphatic spread but still without blood stream dissemination, in whom some hope of cure by local treatment still remains, but these cases are almost impossible to isolate at present and they may respond quite well to irradiation.

The factors of chief importance in judging directions of spread and in estimating the chance of dissemination in clinically early cases, and therefore in planning the best treatment, are: the grade and size of the tumor, the length of history, the site of the tumor, the age of the patient, and the ease with which an opinion on the probability of lymph node involvement can be formed. Two patients with Stage I breast cancers may present totally different pictures: one, for example, may be a woman of fifty-five with a 5 cm. diameter growth in the upper inner quadrant, one month's history, obese and difficult to examine; another may be sixty-five with a 2 cm. diameter growth in the upper outer quadrant, six months' history, slender and easy to palpate. They each require different treatment if they are to get the best chance from their very different prognoses. Standard treatment plans applied rigidly according to the stage alone are a denial of clinical judgement.

Tumor Grade. The future of each patient depends more on the grade of her tumor than on any other factor. Patients with

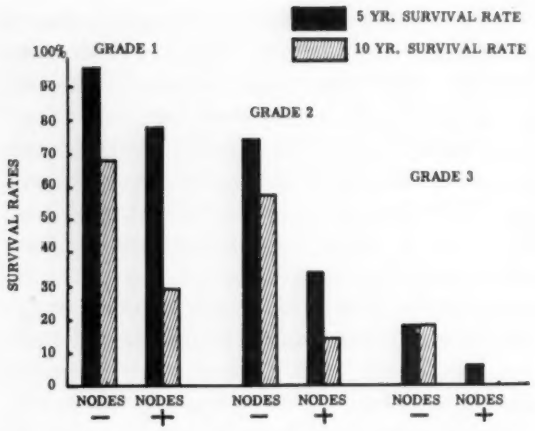

FIG. 4. Survival of new patients with breast cancer by axillary lymph node involvement and grade of tumor activity. Statistics are based on 482 patients seen during 1937–1950 for whom the information was available (Royal Marsden Hospital). (Reproduced with permission.)

Stage I, Grade I tumors who die of their disease have often been mismanaged; few patients with Stage I, Grade 3 tumors survive five years following any treatment, even when the axillary lymph nodes are not involved (Fig. 4). Fortunately, the proportion of Stage I cases in Grade 3 is small (17 per cent in Bloom's[2] series, as compared with 39 per cent in his Stage II cases). Taking Stages I and II together we found Grade I tumors to have axillary lymph nodes involved histologically in 45 per cent, Grade 2 in 70 per cent and Grade 3 in 85 per cent (Table I). Removal of the primary tumor is usually required for certain diagnosis in early breast cancer, so material for tumor grading is nearly always available in these cases. Since local removal of the lump some time before mastectomy can be disastrous and reliable grading by frozen section is unobtainable, an important question still to be answered is how extensive should the operation be in each patient when it must be done before vital information, which should affect the decision, can be made available.

Tumor Size. The size of the tumor is directly related to prognosis. The smaller the tumor the better the prognosis, as would be expected and has been shown by many authors.[5,6,12,23,33] The larger the tumor, the greater the chance of lymph node involvement and of distant metastases and the greater the difficulty in effecting complete local eradication of the primary lesion (Fig. 5). Large tumor size in otherwise early cases, in general, favors limiting the extent of the operation to be performed, because of the greater risks of disseminating the disease and the greater chance that dissemination has already occurred. Much depends, however, on the size of the breast and the risks of failure to remove the whole tumor. Most really large tumors are usually best irradiated before removal is attempted.

Length of History. The influence of length of history on prognosis has surprisingly given rise to a great deal of controversy

TABLE I

SURVIVAL OF PATIENTS WITH OPERABLE BREAST CANCER ACCORDING TO AXILLARY LYMPH NODE INVOLVEMENT AND GRADE OF MALIGNANCY OF TUMOR

(Based on 482 patients seen at The Royal Cancer Hospital 1937–1950 for whom the necessary details were recorded. Graded by Dr. M. Thangavelu)

	Lymph Nodes Not Involved			Lymph Nodes Involved			Proportion of Patients with Lymph Node Involvement (per cent)
	No. of Patients	Five-Year Survival Rate (per cent)	Ten-Year Survival Rate (per cent)	No. of Patients	Five-Year Survival Rate (per cent)	Ten-Year Survival Rate (per cent)	
Grade 1	45	90.6	68.0	37	77.8	29.5	45
Grade 2	96	74.4	57.6	224	34.0	14.9	70
Grade 3	12	28.2	28.2	68	6.2	0.0	85

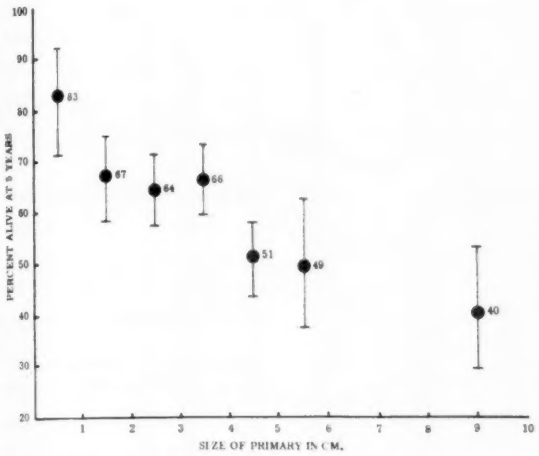

Fig. 5. Prognosis in breast cancer in relation to size of primary tumor in Stages I and II (after McWhirter[23]). Vertical lines show 95 per cent confidence interval for percentage surviving five years.

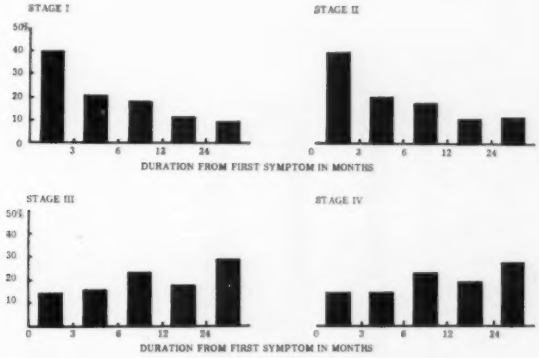

Fig. 6. New patients with breast cancer, 1937–1954. Duration of symptoms in relation to clinical stage (Royal Marsden Hospital). (Reproduced with permission.)

and confusion. It seems obvious that the earlier any particular patient is treated for breast cancer the better; as the disease starts in and spreads from the breast, there must be a time in every case when simple mastectomy can effect a cure. The more rapidly a tumor grows and spreads, the shorter will that time be, and there are some tumors which have already disseminated before they are clinically detectable, but this does not alter the fact that early diagnosis is of value in the remainder or that methods of even earlier diagnosis might not be helpful for the most malignant. If there were any considerable group of patients with nonprogressive cancers of the breast, histologically indistinguishable from the others, a few more patients should be found in Stage I with much longer histories. Patients in the early stages, as would be expected, tend to have a shorter history than those in the later stages (Fig. 6). Survival varies with length of history in Grade 1 and 2, but in Grade 3 the period of life is so short after diagnosis that length of history has little noticeable effect on prognosis (Fig. 7). It is probable that the few Grade 3 cases with a long history had not had tumors in that grade from the start, but had undergone recent progression in malignancy. When the 75 per cent and 50 per cent survival in each stage according to the years after treatment at which each was reached are plotted against length of history in months, a rapid deterioration in result of treatment with increase in history length over the first few months can be seen (Fig. 8). This is most clearly shown in the early case. The patients with such slow growing tumors that they remain a long time in Stage I naturally have a better prognosis than those who reached Stage II or III in the same time. This does not alter the fact that the earlier they are treated the better; it merely shows that with some tumors there is more time to spare. In deciding on treatment policy, however, length of history varies so greatly in accuracy and in importance for prognosis from patient to patient that it must be considered only in relation to stage and grade.

Tumor Site. The comparatively bad prognosis which obtains for inner half as opposed to outer half tumors is confined to the early stages (Fig. 9). It is due to the fact that inner half tumors lead to more frequent involvement of the clinically less easily detectable parasternal lymph nodes.[13] As a result a larger proportion of patients with medial breast tumors who already have lymph node spread are included in Stage I. Inner half tumors in an early stage require special care in treatment planning on this account. They may be un-

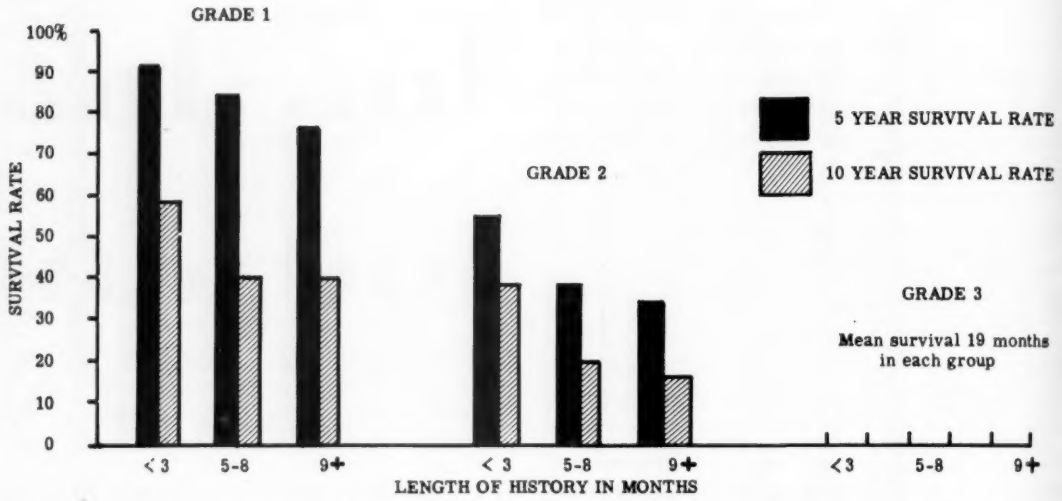

FIG. 7. Survival of new patients with breast cancer by length of history and grade of tumor activity. Statistics are based on 615 patients seen during 1937–1950 for whom the information was available (Royal Marsden Hospital).

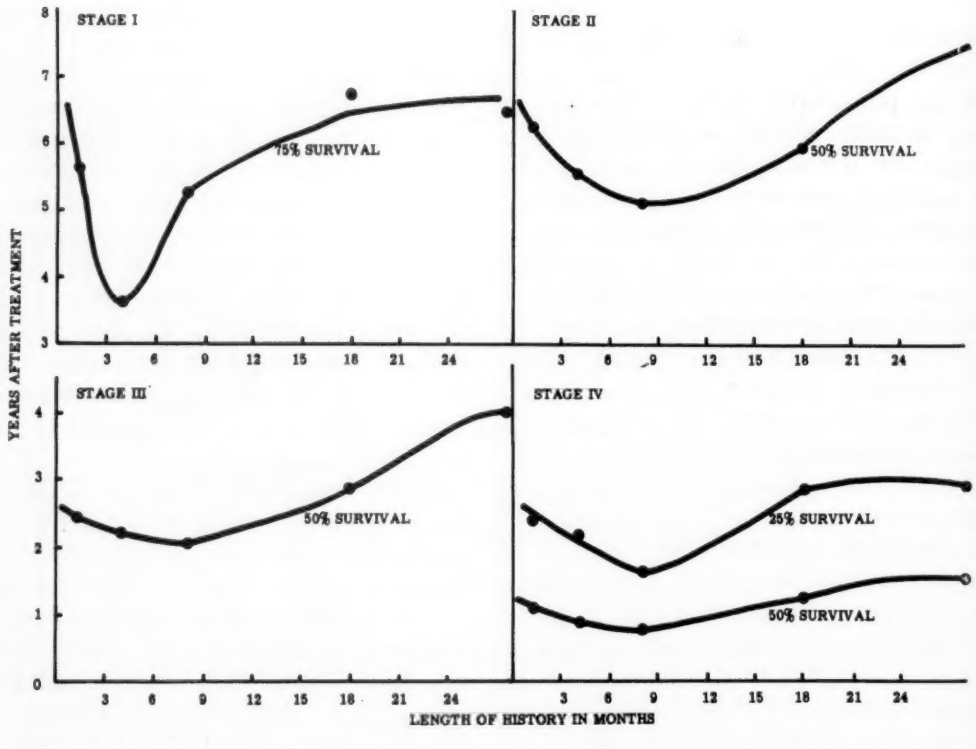

FIG. 8. New patients with breast cancer, 1937–1954. Duration of symptoms by prognosis and stage (Royal Marsden Hospital). (Reproduced with permission.)

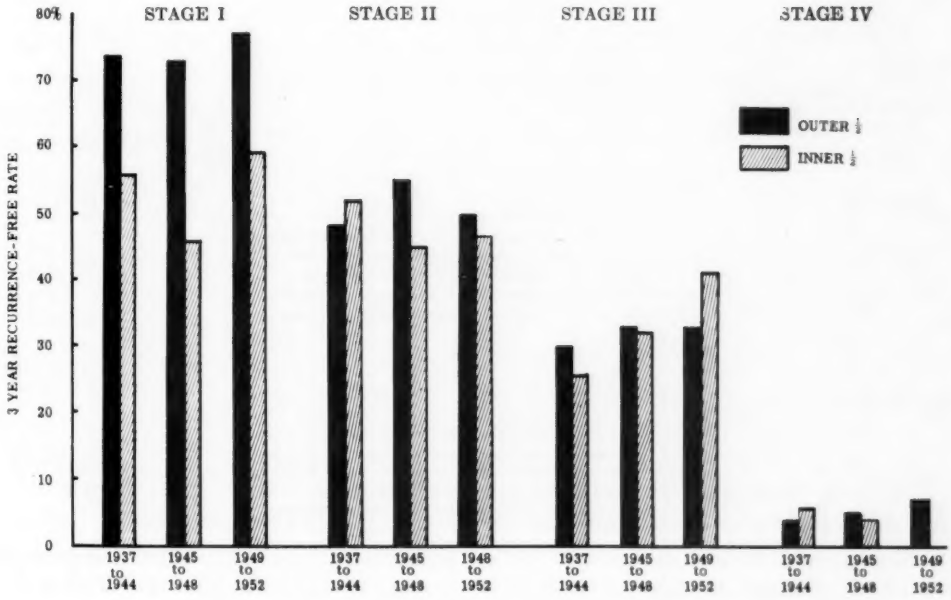

FIG. 9. New patients with breast cancer, 1937–1952. Three year recurrence-free rate by site of primary tumor (Royal Marsden Hospital).

suitable for a radical mastectomy without first giving preoperative irradiation to include the parasternal lymph nodes and to avoid cutting across active lymphatic spread. This is the group which may contain patients suitable for treatment by parasternal lymph node dissection, but no good evidence for its increased efficiency over adequate irradiation has yet been presented. In Stage I carcinomas of the breast, however, the inner half tumors remain the chief treatment problem and the question of preference for surgery or irradiation in the less malignant grades is still undecided.

Age of Patient. Older women tend to wait longer before coming for treatment and have therefore a worse stage distribution than the younger women (Fig. 10). When they do come with early Stage I tumors, they tend to be less thoroughly treated because of their age or infirmity, and, not being able to stand energetic treatment very well, they succumb more easily to intercurrent disease. A large number of elderly women included in any treated group will tend to lower the survival-rate, causing underestimation of the value of the methods used. Because of this McWhirter[21] published separately the results he had obtained in women under sixty-five years of age who had had no evidence of blood stream spread at the time of their treat-

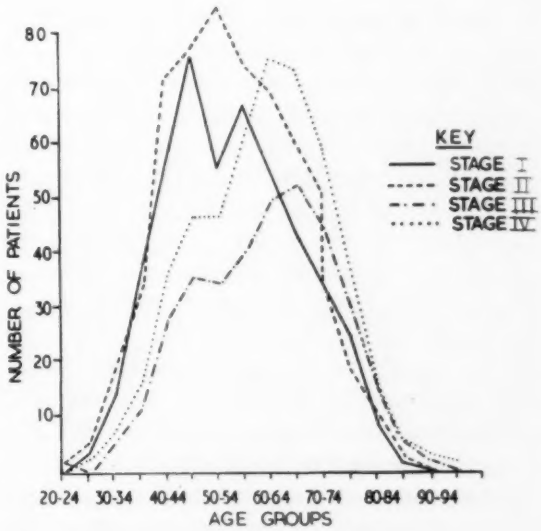

FIG. 10. Carcinoma of the breast, all new patients, 1945–1955 (Royal Marsden Hospital). Stage distribution according to age. (Reproduced with permission.)

TABLE II

NEW PATIENTS WITH BREAST CANCER 1941–1947
COMPARISON OF SURVIVAL RATES IN PATIENTS UNDER 65

Stage	Maximum Crude Five-Year Survival Rate for all Patients under 65 Years of Age at Time of Treatment			
	Royal Infirmary Edinburgh		Royal Marsden Hospital	
	Total	Per Cent Alive	Total	Per Cent Alive
Operable	810	60	373	59
Locally Advanced	369	31	179	31
All Patients without Distant Metastases	1,179	51	552	50

ment (Table II). This selection would seem to reduce the differences between groups treated in different places and throw further doubt on the special virtues claimed for particular treatment plans.

Age also affects prognosis in the young, where hormonal influences are at work so that tumors developing during pregnancy or lactation give a relatively bad prognosis, whereas those arising shortly before the menopause may give a relatively good one.

ANALYSIS OF STAGE I PATIENTS DYING WITHIN TWO YEARS

When we analyze patients in Stage I in whom the tumor grade was known and who, despite the early stage, died within two years of being treated, we find much of interest. From 1937 to 1953 there were 2,648 new patients with breast cancer seen at the Royal Marsden Hospital; 583 (22.0 per cent) were in Stage I and 38 (7.0 per cent) of these died within two years of treatment (Table III). The tumor grade had been recorded in 19 of them (Fig. 11). All 3 patients in Grade 1 had inner half tumors. Two had had a local removal of their primary carcinoma elsewhere before coming to the Royal Marsden Hospital for a mastectomy; in neither case were the axillary lymph nodes involved. The third patient had disease of multicentric origin producing several tumors within the breast. She was difficult to examine and was found at operation to have clinically undetected axillary lymph node involvement. Eight patients were in Grade 2. Three of these had inner half tumors and 2 central tumors. Three patients had tumors of multicentric origin, 2 with involvement of the lymph nodes and in the third they were not examined. Two had histories of under one month, outer half tumors of 2.0 cm. and 2.3 cm. diameter and negative lymph nodes, giving no reason to suspect disaster. Both developed liver metastases. One had a history of more than one year, preoperative irradiation, no axillary lymph node involvement, but extensive local invasion of perivascular and perineural lymphatics. She developed metastases in bone and liver. Eight patients were in Grade 3. Five had inner half tumors, all had short

TABLE III

ROYAL MARSDEN HOSPITAL
CARCINOMA OF THE BREAST 1937–1953

Stage I

Total Seen: 583
Dying within Two Years: 38 (7 Per Cent)
Grade of Tumor Known in 19

Grade	No.	Difference from Expected No.	
1	3	0	2: Local excision before mastectomy 1: Multicentric origin
2	8	−5	
3	8	+5	

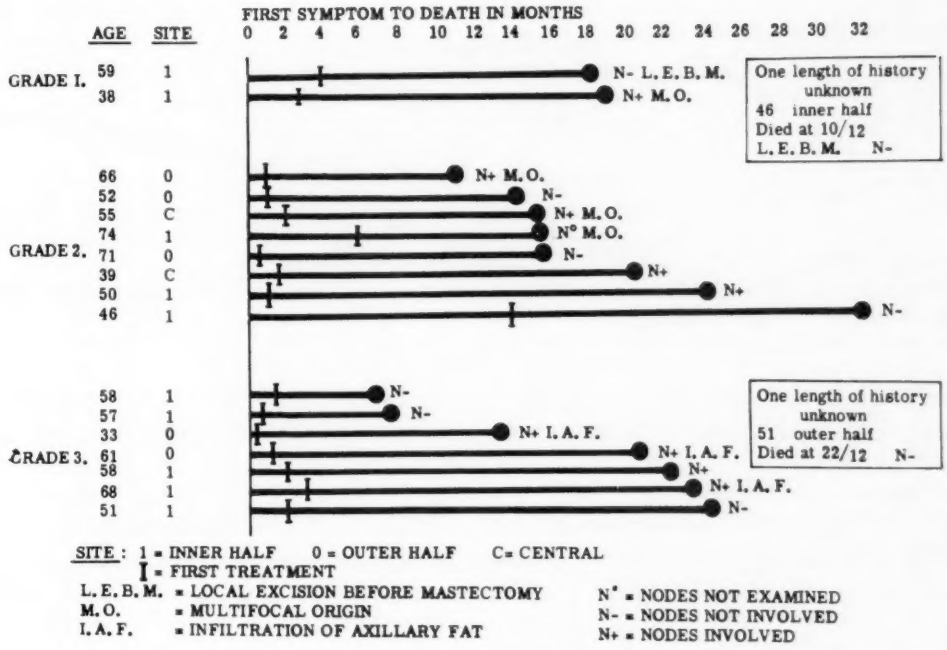

FIG. 11. Carcinoma of the breast, 1937–1953. Stage I cases dying within two years of treatment. Nineteen graded out of 38 dead (Royal Marsden Hospital).

histories of less than three months, 3 had no axillary lymph node involvement, and 3 had lymph node metastases with infiltration of axillary fat.

The preponderance of inner half tumors (11 out of 19, with 2 more placed centrally) is striking. The dangers of inadequate surgery for diagnosis and of multiplicity of primary tumors are suggested. Two out of the only 3 patients with Stage I, Grade I tumors who died within two years of treatment had had local removals of lumps thought to be innocent, followed by a delay of several days in one case and a few weeks in the other before a mastectomy was performed. All 38 died with distant blood-borne metastases with a predominance of the quickly killing liver and brain deposits.

Most of these patients usually recover if well treated and a few will die whatever is done locally. More and more radical operations do not save the few who have metastases already and may hasten dissemination in borderline cases. Axillary dissection is still the most effective method of dealing with this most common direction of spread, however, and radical mastectomy achieves excellent results in carefully selected patients. The differences between treatment plans in early cases are small, and depend more on quality of material treated than on the method used. An approach based on what is judged to be best for each patient after careful study of the individual circumstances, and employing radical mastectomy, local mastectomy, preoperative and postoperative irradiation each when indicated, is likely to yield better results than any fixed treatment plan. The limitation on possible improvement with any combination of local methods remains, however; if they are to succeed, the disease must still be localized.

LONG SURVIVAL IN ADVANCED CASES

With advanced cases the likelihood of survival with any present treatment method is small because in the majority the tumor cells have already been disseminated so that the chance of cure with surgery or radiation therapy has often gone (Table IV). The reported five-year survival-rates

TABLE IV

ROYAL MARSDEN HOSPITAL
NEW PATIENTS WITH BREAST CANCER 1940–1949
TOTAL SEEN 1,454

	Total	Per Cent of Total Seen	Surviving			Per Cent Surviving Five Years and More
			Three Years	Four Years	Five Years and More	
Stage III	378	25.9	166	131	104	27.5
Stage IV	293	20.1	21	12	11	3.8

even in Stage III vary only from 10 per cent to 30 per cent and in Stage IV from 0 to 10 per cent (Table V).

The late stages contain the locally advanced and the widely disseminated tumors, as assessed clinically before treatment. These two groups overlap a good deal since a high proportion of patients with locally advanced disease already have distant metastases when first seen, even if they are not clinically detectable. Although little improvement in results has been noted in the early stages in the last few years, there has been an improvement with Stage III cases (Fig. 12). This is unlikely to have been due to the transfer to Stage III of some late Stage II cases, since if this were so the Stage II results should have shown a corresponding improvement. A small group of locally advanced cases still without blood stream spread do, however, reach the hospital while they retain a chance of cure by local methods. It is the recognition of the possibility of success with this group and the attempt to pick them out and treat them radically which has been chiefly responsible for this improvement. In some centers more extensive surgery, with dissection of the parasternal and supraclavicular lymph nodes as well as those in the axilla, has been adopted. Our own tendency has been to operate on fewer of these patients and to make the operations that are done less radical. Reliance is placed first on irradiation. In those cases where a radical mastectomy is performed, it usually follows a course of preoperative irradiation given to reduce the risk of dissemination. Local mastectomy may be done before irradiation in patients with extensive lymph node involvement but with small primary tumors, especially when the breast is very large.

The chief problems in the treatment of

TABLE V

ABSOLUTE FIVE-YEAR SURVIVAL RATES IN LATE STAGES OF BREAST CANCER

Author and Year of Publication	Years in Which Patients Were First Treated	Total of New Patients Seen in Period	Absolute Five-Year Survival Rates	
			Stage III	Stage IV
Windeyer[40] (1949)	1936–1942	1,091	26	7
Smithers *et al.*[32] (1952)	1937–1944	1,093	19	7
Umberto[37] (1952)	1931–1946	274	24	0
Shimkin *et al.*[30] (1952)	1918–1944	1,056	18	0
Williams *et al.*[39] (1953)	1930–1939	1,044*	10	1
McWhirter[22] (1955)	1941–1947	1,882	30	4
Royal Marsden Hospital	1940–1949	1,454	28	4

* This total excludes 60 cases with incomplete records.

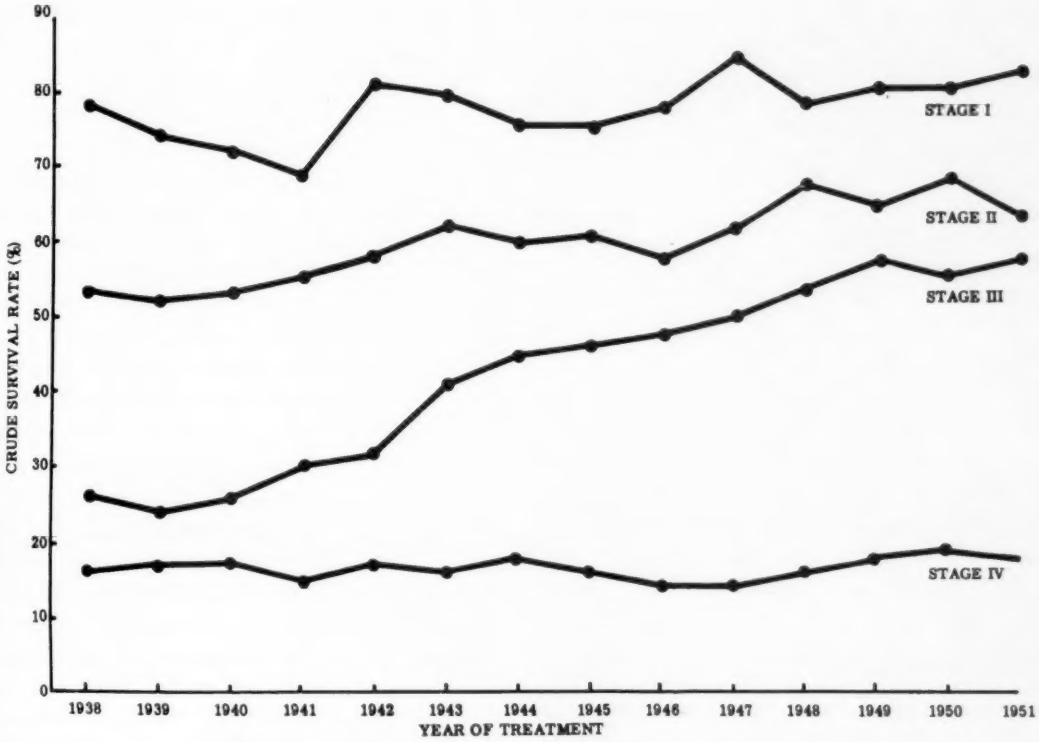

FIG. 12. New patients with breast cancer, 1938–1951. Trends in crude three-year survival-rates by stage and year of treatment. (Each point represents the aggregate result for three successive years and is plotted at the mid-year.) (Reproduced with permission.)

advanced breast cancer center, first, on attempts to select those patients still curable by local means and, second, upon trying to learn when it is most profitable to use which hormone treatments. The control of disseminated disease, even if temporary, even if only in a small proportion of all the patients seen, is nevertheless general control of disseminated cancer. As such it approaches the long sought solution to the main treatment problem of one of the major malignant diseases and so provides a new hope for the future.

Grade, Size, Site and Length of History. In late, as with early, cases the prognosis still depends on grade, size and site of the primary tumor, the length of history and the age of the patient.

Grade is only known when a mastectomy has been done. Since most late cases are inoperable, and removing a piece for biopsy for grading is usually inadequate and may be dangerous, the grade in late cases is rarely known. The probable tumor grade has usually to be assessed from the other signs which indicate the rate of growth and spread. Few patients with advanced Grade 3 tumors survive for long. Hormone therapy is their hope, but palliative surgery and radiation therapy for relief of symptoms should not be neglected.

Size is of importance in that the larger the primary tumor and the smaller the breast, the greater the reason for rejecting surgery as the first treatment method to be used. Failure to remove the whole primary tumor and the immediate local lymphatic permeation usually makes matters worse and leads, at times, to that surgical disease of plaque-like chest recurrence, which is so distressing and so difficult to deal with (Fig. 13).

FIG. 13. Photograph showing chest recurrence after failure to remove the whole primary tumor and local lymphatic permeation.

Site alone has little influence on the decision to attempt radical treatment in advanced cases, but there is possibly a rather better chance and rather more indication for surgery with outer half tumors.

The history is usually longer than it is in the early cases, but an unusually long history, still without evidence of any blood stream spread, may encourage a more energetic treatment attempt. Nevertheless, most of the longer survivors in the late stages have the shorter histories (Fig. 14).

Mode of Spread. With late cases mode of spread is extremely important. So long as it is confined to the lymphatic pathways some hope from local therapy remains. It is frequently difficult to know whether involvement of lymph nodes in the contralateral axilla or supraclavicular fossa is due to spread across the midline or to the presence of a new primary tumor in the opposite breast. Bilateral breast cancer is certainly quite common,[9] but with communicating lymphatics, metastases on the opposite side can easily occur. The important point is that patients with bilateral involvement of the axillary or supraclavicular lymph nodes may sometimes survive many years if radically treated. Involvement of parasternal lymph nodes may here be deceptive since they frequently erode the sternum and so may be mistaken for blood-borne metastases. An example of a good result with tumor spread to the sternum is a patient who was aged fifty-four when treated in 1943 (Fig. 15*A*). She had a mass in the outer half of the right breast, large hard lymph nodes in both axillae (one of which was removed for biopsy) and both supraclavicular fossae, an enlarged left infraclavicular lymph node and a parasternal mass invading the bone. She had roentgen treatment only and is still alive and well fourteen years later (Fig. 15*B*). A few long term survivors in Stage III are shown by grade in Table VI.

Age and Menopause. With advanced disease the influence of age is of special interest. The menopause would seem to be the key to the question of variation of prognosis and response to hormone therapy with age. The risk of developing breast cancer increases fairly steadily with age, but a departure from the trend between the ages of

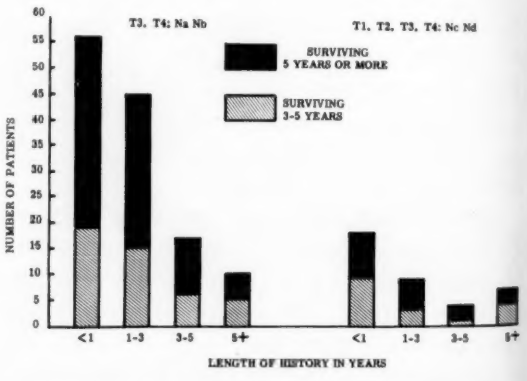

FIG. 14. New patients with Stage III breast cancer, 1940–1949. One hundred and sixty-six survived more than three years out of 378 seen. (Reproduced with permission.)

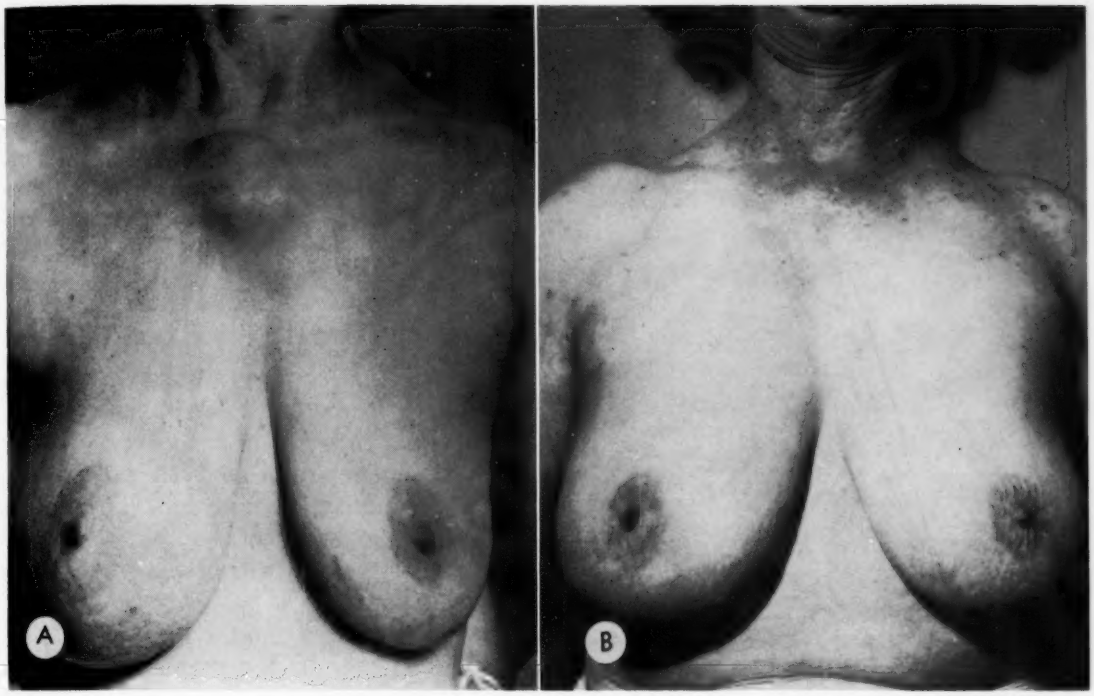

Fig. 15. (*A*) Female, aged fifty-four. When seen in 1943, she had a mass in the outer half of the right breast, large hard lymph nodes in both axillae and in both supraclavicular fossae, an enlarged left infraclavicular lymph node and a parasternal mass invading the bone. (*B*) Same patient after irradiation only, alive and well fourteen years later. (Reproduced with permission.)

fifty and sixty has been observed (Fig. 16).[4,18,31,32] Clemmesen[4] had made the interesting observation that this feature was more marked in single than in married women. In 1939 Evans and Leucutia[8] noted the relatively poor results following treatment for breast cancer at the ages of fifty to fifty-nine; this has since been confirmed by others.[28,32] There has been much speculation about the meaning of these observations. Clemmesen[4] thought they indicated the presence of two different kinds of breast cancer, sensitive to female hormones in different degrees. Smithers[31] suggested that

Table VI

ROYAL MARSDEN HOSPITAL
NEW PATIENTS WITH BREAST CANCER 1940–1949
(Survival by grade in Stage III substages in 64 cases graded out of 166 patients surviving three years or more)

Substage	No. Surviving Three Years or More	No. Graded	Grade 1	Grade 2	Grade 3
T_3 or T_4:Na	41	20	5 (190+)	14 (168)	1 (37)
T_3 or T_4:Nb	87	30	5 (108+)	20 (170+)	5 (132+)
T_1 or T_2:Nc or Nd	10	6	2 (204+)	4 (156+)	0
T_3 or T_4:Nc or Nd	28	8	2 (66)	5 (96+)	1 (139+)
Totals	166	64	14	43	7

Figures in parentheses show the longest survival in months in each group.
+ = still alive.

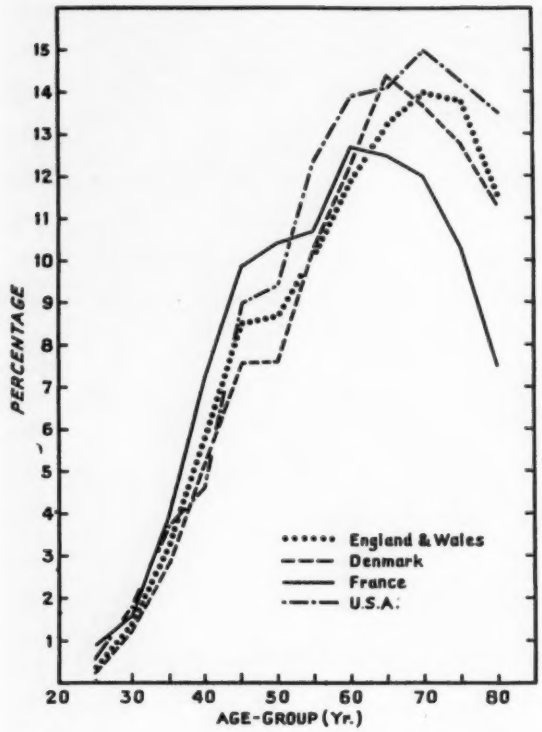

FIG. 16. Breast cancer morbidity (McKenzie[18]).

the natural menopause might exert a beneficial effect on some patients who had developed breast cancer but in whom it had not yet been detected, which may be the same thing. Such spontaneous regression might lead to delay both in diagnosis and in death in a sufficient number of patients developing breast cancer just before the menopause to distort the curve. The kink may be unrelated to hormone response, being due to the superimposition of curves due to two tumor types, one in which the force of mortality increases indefinitely with advancing age and one in which a maximum is reached at or near the age of the menopause and occurs more commonly in nulliparous women. Remarkable regression is, however, known to take place at the natural menopause at times and the few reported cases remain the longest hormone induced remissions known.[31] Most reports of spontaneous regression of breast cancer have been in women of menopausal age (Table VII). Some of the best therapeutic hormone responses have been obtained in pre-menopausal women. Some of the long survivals following local treatment to distant metastases may be due to the fortunate occurrence of a natural menopause to which too little significance has been allowed in the past (Fig. 17).

ANALYSIS OF STAGE IV PATIENTS LIVING MORE THAN THREE YEARS

A study of 293 Stage IV breast cancer patients seen from 1940 to 1949 showed that 21 survived three years or more; 9 of these were pre-menopausal and 12 post-menopausal by more than ten years. There were no three year survivors among the Stage IV patients treated within ten years after the menopause.

Seven out of the 9 in the pre-menopausal group (Fig. 18) had a menopause at the start of treatment (2 spontaneous, 3 roentgen ray induced, 1 by oophorectomy and 1 by androgen treatment). Three of them were still alive thirteen, ten and nine years afterwards (2 with no further treatment other than the initial roentgen therapy and menopause; one at ten years after the whole therapeutic gamut of oophorectomy, adrenalectomy, hypophysectomy, radical mastectomy, testosterone injections and further irradiation). Two out of the pre-menopausal group were treated, rather surprisingly, with estrogens at the time of their initial roentgen therapy.

The response of some older women to estrogen treatment is another point of special interest. This is the other group in which we found a few patients with advanced disease who had survived a long time (Fig. 19). Eight out of the 12 surviving three years or more had estrogens, all had roentgen therapy, one a local mastectomy as well as part of the initial treatment, but nothing other than estrogens later. One died nine years and two months after treatment at the age of eighty-four with cardiac failure. The predominant feature in these cases, particularly in the late

TABLE VII

SPONTANEOUS REGRESSION OF CANCER OF THE BREAST

Case No.	Age	Course	Period of Observation	Author
1	39	Regression of axillary masses and of local recurrence	9 wk.	Mackay[17]
2	37	Regression of enlarged neck lymph nodes, of liver metastases and of local recurrence	4 yr.	Hodenpyl[14]
3	61	Regression of local recurrence	7 yr.	Lilienthal[16]
4	40	Regression of liver metastases and of local recurrence	—	Scott[29]
5	53	Regression of pleural deposits and absorption of effusion	5 yr.	Nohrman[25]
6	46	Regression of ulcerated primary tumor, of enlarged lymph nodes and of subcutaneous nodules	2 yr.	Smithers[31]
7	46	Regression of primary tumor. Recurrence in axilla 17 years later	17 yr.	Smithers[31]
8	46	Regression of primary tumor. Metastases to bones 14 years later	14 yr.	Smithers[31]

In Cases 6, 7 and 8 regression occurred at menopause. In Cases 1, 2 and 4 regression possibly occurred at menopause. In Case 3, there was no relationship to menopause. Case 5 had a nine-year history; ovarian metastases were found at autopsy.

post-menopausal group, is the frequency of detection of extensive lymphatic spread compared with that of blood-stream dissemination.

CONCLUSIONS

A study of failure with early breast cancer and success with advanced disease brings out many interesting observations. In early cases failure is usually due to distant blood-borne metastases. Mastectomy is the first method of choice in early cases, being necessary for diagnosis and grading as well as the most certain treatment for well localized disease; the decision as to its extent should be taken on the merits of each case. Points favoring a bad prognosis should limit not extend the use of surgery, which, if it does not succeed completely, may well make matters worse. Large medial tumors with a short history are, however, the only ones in which irradiation before mastectomy is often indicated in Stage 1, especially when the patient is obese and difficult to examine.

All patients with inner half tumors and all with outer half tumors with histologic involvement of axillary lymph nodes should have postoperative irradiation to axillary, supraclavicular and parasternal lymph nodes, especially if Grade 2 or 3. In all young women before the menopause who have Grade 3 tumors, multicentric origin, extensive perivascular or perineural lymphatic permeation or involvement of axillary fat, an artificial menopause should be considered as part of the first planned treatment.

In some late cases success may be achieved in the pre-menopausal group if a menopause is induced and energetic irradiation employed, especially if the spread is by lymphatics rather than by blood vessels. In the elderly, estrogen treatment com-

FIG. 17. Female, aged 42, treated by roentgen therapy for a bony metastasis at the time of her natural menopause. Symptom-free for five years, then developed other metastases. (Reproduced by permission.)

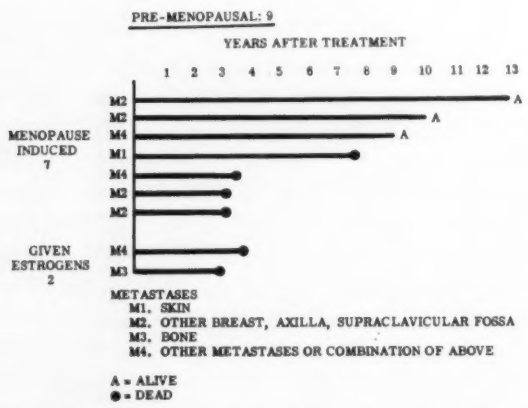

FIG. 18. Carcinoma of the breast Stage IV (Royal Marsden Hospital). Twenty-one patients survived three years or more after treatment out of 293 in Stage IV from 1,454 seen, 1940–1949. Premenopausal group: 9 cases. (Reproduced with permission.)

bined with irradiation may also give some long-term survivals.

Adrenalectomy, hypophysectomy and radioactive pituitary implants have all produced dramatic regressions, even with widespread blood stream metastases. They all have their own difficulties and complications, however. Time is still required for the assessment of their value, which must be weighed against their disadvantages. The careful selection of patients most likely to benefit by each method or their combination to reduce the amount of unnecessary suffering which may be inflicted is of greatest significance. These methods hold out such a tempting prospect of control of disseminated disease, the great unsolved problem of breast cancer therapy, that they are

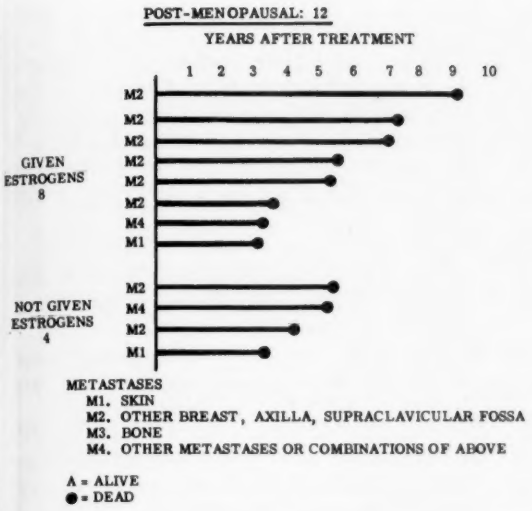

Fig. 19. Carcinoma of the breast Stage IV (Royal Marsden Hospital). Twenty-one patients survived three years or more after treatment out of 293 in Stage IV from 1,454 seen, 1940–1949. Post-menopausal group: 12 cases. (Reproduced with permission.)

of immense potential importance for the future. We must still assess their present value for each patient in the light of what we may achieve with less drastic measures.

Radiotherapy Department
The Royal Marsden Hospital
Fulham Road
London, S.W. 3, England

I am most grateful to my Surgical and Radiotherapy colleagues of the Royal Marsden Hospital for allowing me to report the results of my investigations of all the patients with breast cancer attending.

Figures 3, 4, 6, 8, 10, 12, 14, 15, 17, 18, and 19 are reproduced with the kind permission of Professor Lucio Severi, Editor of the *Proceedings of the II International Symposium on Mammary Cancer.*

REFERENCES

1. Berven, E. Treatment and results in cancer of breast. Am. J. Roentgenol. & Rad. Therapy, 1949, *62*, 320–325.
2. Bloom, H. J. G. Prognosis in carcinoma of breast. *Brit. J. Cancer*, 1950, *4*, 259–288.
3. Case, R. A. M. Cohort analysis of cancer mortality in England and Wales, 1911–1954 by site and sex. *Brit. J. Prev. & Soc. Med.*, 1956, *10*, 172–199.
4. Clemmesen, J. On etiology of some human cancers. *J. Nat. Cancer Inst.*, 1951, *12*, 1–21.
5. Dahl-Iversen, E. Carcinoma mammae. *Ugeskr. f. Laeger*, 1930, *92*, 1090.
6. Eggers, C., de Cholnoky, T., and Jessup, D. S. D. Cancer of breast. *Ann. Surg.*, 1941, *113*, 321–340.
7. Engelstad, R. B. Surgical and radiation treatment of cancer of breast. Am. J. Roentgenol. & Rad. Therapy, 1948, *60*, 776–787.
8. Evans, W. A., and Leucutia, T. Deep roentgen-ray therapy of mammary carcinoma. III. Fifteen year results in a formerly published group and statistical analysis of 1,200 cases treated between 1922 and 1937. Am. J. Roentgenol. & Rad. Therapy, 1939, *42*, 866–882.
9. Farrow, J. H. Bilateral mammary cancer. *Cancer*, 1956, *9*, 1182–1188.
10. Haagensen, C. D., and Stout, A. P. Carcinoma of breast; results of treatment. *Ann. Surg.*, 1942, *116*, 801–815.
11. Haagensen, C. D. Treatment and results in cancer of breast at Presbyterian Hospital, New York. Am. J. Roentgenol. & Rad. Therapy, 1949, *62*, 328–334.
12. Haagensen, C. D. Self-examination of breasts. *J.A.M.A.*, 1952, *149*, 356–360.
13. Handley, R. S., and Thackray, A. C. Internal mammary lymph chain in carcinoma of breast. Study of 50 cases. *Lancet*, 1949, *2*, 276–278.
14. Hodenpyl, E. Treatment of carcinoma with body fluids of recovered case. Preliminary communication. *Med. Rec.*, 1910, *77*, 359.
15. Kaae, S. Radiotherapy in cancer of breast with particular reference to value of preoperative irradiation as supplement to radical mastectomy. Analysis of 1418 new cases. *Acta radiol.*, 1952, Suppl. 98.
16. Lilienthal, H. Disappearance of secondary carcinoma without extirpation. *Internat. J. Surg.*, 1913, *26*, 156.
17. Mackay, C. G. Case that seems to suggest clue to possible solution of cancer problem. *Brit. M. J.*, 1907, *2*, 138.
18. McKenzie, A. Cancer of female breast, mortality and menopause. *Lancet*, 1955, *2*, 1129–1130.
19. McKinnon, N. E. Cancer mortality trends under different control programs. *Canad. J. Pub. Health*, 1950, *41*, 7–14.
20. McWhirter, R. Value of simple mastectomy and radiotherapy in its management. *Brit. J. Radiol.*, 1948, *21*, 599–610.
21. McWhirter, R. Basic information required in

presentation of results. *Acta radiol.*, 1954, Suppl. 116, p. 136–140.

22. McWHIRTER, R. Simple mastectomy and radiotherapy in treatment of breast cancer. *Brit. J. Radiol.*, 1955, *28*, 128–139.
23. McWHIRTER, R. Some factors influencing prognosis in breast cancer. *J. Fac. Radiologists*, 1957, *8*, 220–234.
24. NOHRMAN, B. A. Cancer of breast. Clinical study of 1042 cases treated at Radiumhemmet, 1936–1941. *Acta radiol.*, 1949, Suppl. 77.
25. NOHRMAN, B. A. Spontaneous regression of pleural carcinosis. *Acta radiol.*, 1950, *33*, 12–15.
26. PHILLIPS, A. J., and OWCHAR, M. Mortality Trends in Canada for Various Sites of Cancer. Toronto, 1955.
27. PHILLIPS, A. J., and OWCHAR, M. Cancer mortality in various countries. *Bull. World Health Organ.*, 1957, *16*, 267.
28. RICHARDS, G. E. Mammary cancer: place of surgery and radiotherapy in its management; study of some of the factors which determine success or failure in treatment. *Brit. J. Radiol.*, 1948, *21*, 109–127.
29. SCOTT, J. B. Spontaneous regression of cancer. *Brit. M. J.*, 1935, *1*, 230.
30. SHIMKIN, M. B., LUCIA, E. L., STONE, R. S., and BELL, H. G. Cancer of breast. Analysis of frequency, distribution and mortality at University of California Hospital, 1918 to 1947, inclusive. *Surg., Gynec. & Obst.*, 1952, *94*, 645–661.
31. SMITHERS, D. W. Cancer of breast and menopause. *J. Fac. Radiologists*, 1952, *4*, 89–96.
32. SMITHERS, D. W., RIGBY-JONES, P., GALTON, D. A. G., and PAYNE, P. M. Cancer of breast. A review. *Brit. J. Radiol.*, 1952, Suppl. 4.
33. STEWART, F. W. Tumors of breast. *In:* Atlas of Tumor Pathology. Section 9. Fascicle 34. Armed Forces Institute of Pathology, Washington, 1950.
34. STOCKS, P. Studies of cancer death rates at different ages in England and Wales in 1921 to 1950. Uterus, breast and lung. *Brit. J. Cancer*, 1953, *7*, 283–302.
35. TAYLOR, G. W. Treatment and results in cancer of breast. AM. J. ROENTGENOL. & RAD. THERAPY, 1949, *62*, 341–344.
36. TRUSCOTT, B. M. Carcinoma of breast. Analysis of symptoms, factors affecting prognosis, results of treatment and recurrences in 1211 cases treated at Middlesex Hospital. *Brit. J. Cancer*, 1947, *1*, 129–145.
37. UMBERTO, B. Cancro della mammella. Considerazioni statistiche e risultati lontani. *Tumori*, 1952, *38*, 289–312.
38. WATSON, T. A. Results of treatment of cancer of breast. *Surg., Gynec. & Obst.*, 1957, *104*, 106–112.
39. WILLIAMS, I. G., MURLEY, R. S., and CURWEN, M. P. Carcinoma of female breast: conservative and radical surgery. *Brit. M. J.*, 1953, *2*, 787–796.
40. WINDEYER, B. W. Cancer of breast. AM. J. ROENTGENOL. & RAD. THERAPY, 1949, *62*, 345–354.

NEUROBLASTOMA ORIGINATING FROM OLFACTORY EPITHELIUM (ESTHESIONEUROBLASTOMA)*

By PAUL A. RIEMENSCHNEIDER, M.D., *and* JOHN T. PRIOR, M.D.
SYRACUSE, NEW YORK

THERE have been frequent reports of the occurrence of primary intranasal nerve tumors including particularly gliomata and neurofibromata. The occurrence of primary intranasal neuroblastomata has, however, not been widely reported in the English literature. In 1924 Berger, Luc and Richard[2] described such a tumor and since this time scattered reports have appeared throughout the European literature.[3,5,7–11,14,15] Schall and Lineback[12] in 1951 collected 14 cases from the literature and added 3 more of their own and this constitutes the only available report in English.

This tumor has been termed "esthesioneuroblastoma" by European authors. It apparently arises totally independent of the central nervous system in the nasal fossa with a probable origin in the olfactory placode.

Because of the paucity of reports of similar tumors in the English literature and because of the unique method of metastatic spread of this tumor, the following case report seems to be of considerable interest.

FIG. 1. Caldwell projection of the nasal sinuses showing the massive opacification of the ethmoid cells. There has been bone destruction involving the cell septa and the wall of the orbit on the left side.

REPORT OF A CASE

W. C., a sixty-seven year old white man, was first seen in February, 1956, at which time he complained of pain in his forehead, numbness of the left side of his lip and diplopia. In addition, over a period of a month he had noticed progressive protrusion of his left eye. Examination at this time demonstrated a visible mass in the left nostril which was red and firm. There was also a total left ophthalmoplegia. Roentgenograms of the sinuses were obtained (Fig. 1–3) which showed a soft tissue mass in the nose and nasopharynx as well as clouding and bone destruction involving the ethmoids on both sides. A biopsy was obtained. Microscopic examination of this material disclosed the presence of large areas of tumor, generally arranged in sheets and located beneath an intact nasal mucous membrane (Fig. 4). The individual tu-

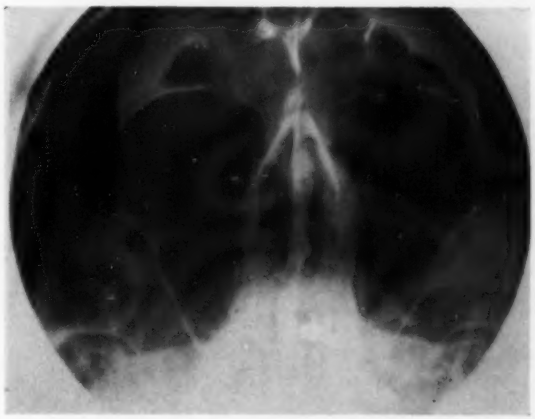

FIG. 2. Waters' projection of the nasal sinuses showing similar change.

* From the Departments of Radiology and Pathology, State University of New York, Upstate Medical Center, Syracuse, New York.

FIG. 3. Submentovertical roentgenogram of the base of the skull demonstrating the large soft tissue mass in the nasal fossa and extending posteriorly into the nasopharynx. No definite bone destruction of the base of the skull could be identified at this time.

mor cells tended to be round or spindle-shaped and were characterized by scanty acidophilic-staining cytoplasm and indistinct cell borders. While the nuclei showed considerable variation in size, shape, and in amount of nuclear chromatin, in general, they were vesicular with occasional large nucleoli being recognized. Cellular necrosis was not present, and there was rather marked desmoplasia. Evidence of lymphatic vessel invasion was present. The microscopic interpretation of the tumor at this time was "anaplastic epithelial type carcinoma, presumably of transitional cell type."

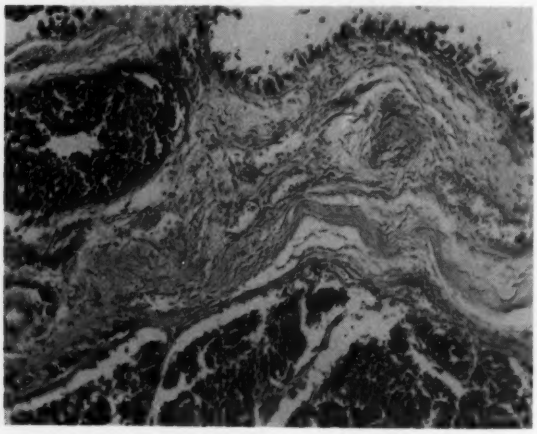

FIG. 4. Biopsy from the ethmoid region showing subepithelial foci of tumor originally interpreted as transitional cell carcinoma. ×127.

Following the report of this biopsy the patient was referred to one of us (P.A.R.) for deep roentgen therapy. He was treated through 5 portals aimed at the mass in the nose and nasopharynx over a period of six weeks to a total estimated tumor dose of approximately 6,000 r. The therapy was carried out at 220 kv., 15 ma., a half-value layer of 2 mm. of copper and a target-skin distance of 50 cm. Each portal was 6 by 8 cm. in size. By April, 1956 there was marked improvement in the patient's ophthalmoplegia and a considerable improvement in vision. The pain and numbness of which the patient previously complained had totally disappeared. No gross mass was visible in the nose or nasopharynx at this time. By May, 1956 the patient's skin had healed well in the areas where there had been radiation reaction. There was a slight lateral strabismus but gross examination showed no definite evidence of tumor. Roentgenograms of the sinuses at this time no longer showed evidence of a mass. In July of 1956 the patient began to complain of sacral and coccygeal pain with sphincter incontinence. Roentgenograms of the pelvis showed Paget's disease of the left innominate bone. No destructive lesions were evident in the pelvis or sacrum. The patient, however, went progressively downhill and was admitted to the hospital with acute urinary retention. At this time there was slight exophthalmos and ptosis. The left patellar reflex was absent. Straight leg raising caused pain at 30 degrees bilaterally. There was moderate weakness of the lower extremities which was equal bilaterally. There was a diminution of touch in the first and second sacral segments and of pain in the fifth sacral segment. Position sense was intact. There was absent vibratory sense in the toes and over the sacrum. The reflexes were diminished in the lower extremities. There was a flexor plantar response. On the basis of this examination it was felt that an intraspinal lesion was present and a lumbar puncture was done. A needle was introduced at the third lumbar interspace. There was no evidence of block. The fluid was xanthochromic and under a pressure of 190 mm. Hg. Three cubic centimeters of pantopaque were introduced and myelography performed (Fig. 5 and 6). Under fluoroscopic control there was seen relatively little motion of the opaque ma-

terial and it was felt that the majority of it was subdural in location. There were, however, multiple filling defects within the filled column. The significance of these irregularities was not recognized because it was felt that the opaque material was subdural in location. The patient went progressively downhill and expired on August 15.

Necropsy (A-56-202) was performed five and one-half hours after death. The most significant findings were limited to the central nervous system. The brain weighed 1,450 gm. and upon its removal a 3 cm. mass lying on the cribriform plate of the ethmoid beneath the dural membranes was noted. The mass was white in color and was rather necrotic and soft in consistency. This tumor mass extended through the cribriform plate into the superior nasal conchae and had also spread laterally along the lateral walls of the orbit. There was erosion of the bones of both orbital cavities, more marked on the right side. The finger could be thrust from the anterior cranial fossa through the nasal cavity and into the soft tissue on the wall of the orbit on both sides. The spinal cord was removed and from the level of L5 to D12 there were discrete firm masses attached to both the cord and the cauda equina. These were most numerous in the region of L4 (Fig. 7). The masses never coalesced but they effectively blocked the cord at L4. These masses were pinkish-white and purple in color, and measured from 0.2 cm. to 0.7 cm. in diameter. There appeared to be no gross evidence of invasion of the wall of the bony spinal column or of the dura.

Examination of the external surface of the

Fig. 5. Anteroposterior roentgenogram during myelography. The opaque material extends over a considerable distance with nodular defects within it. Because of the lack of mobility and the peculiar distribution of the opaque material, it was felt that much of it was subdural. In actual fact, the opaque material is spread about the tumor of the cauda equina with the nodules representing the individual tumor masses.

Fig. 6. Lateral view of the myelogram showing similar changes and demonstrating the nodules of the cauda equina to better advantage.

FIG. 7. Cauda equina showing the nodular masses of metastatic tumor surrounding the nerves and accounting for the roentgenographic appearance shown in Figures 5 and 6.

brain and the leptomeninges was not unusual. Cut sections of the cerebral hemispheres disclosed several lesions. There was a reddish-brown mass of tissue which measured 1.1 cm. by 0.2 cm. by 0.6 cm. in the right superior frontal gyrus within the white matter. It did not extend to the cortex on either side of the gyrus. A second lesion which was irregular in outline, grayish-brown speckled in appearance, measuring 0.7 cm. by 0.5 cm. by 0.8 cm. was located in the genu of the corpus callosum extending just to the outer border of the cortex of the cingulate gyrus. It extended approximately one-half way through the corpus callosum at this point. Approximately 1 cm. lateral to this lesion there was a third similar but separate area measuring 0.8 cm. in diameter and located in the medial aspect of the centrum semiovale but within the outgoing fibers of the corpus callosum. Another lesion with a somewhat similar gross appearance, except for a more intense red color, was located in the left superior temporal gyrus, and measured 1 cm. by 1 cm. by 0.6 cm. This lesion extended from the white matter through the corticomedullary junction and approximately one-half way through the cortex at this point. Sections of the cerebellum and brain stem showed no gross abnormalities.

Other gross findings included evidence of an old septal myocardial infarction, prostatic hypertrophy, pulmonary emphysema, pleural and pericardial effusions and some pulmonary congestion.

The impression of the prosector at this time was that the case was a primary carcinoma in the region of the ethmoid sinuses with erosion of bone and invasion of the nasal, cranial, and orbital cavities. The tumor about the spinal cord was thought to be metastatic although an ependymoma could not be ruled out. The cerebral lesions were felt to be metastatic from the primary nasal tumor.

With the examination of the microscopic sections obtained from the brain and spinal cord at necropsy, it became apparent that the tumor was probably not of nasal epithelial origin. Sections taken from the left superior temporal gyrus of the brain showed some infiltration of the cerebral substance but there was very marked infiltration of the tumor

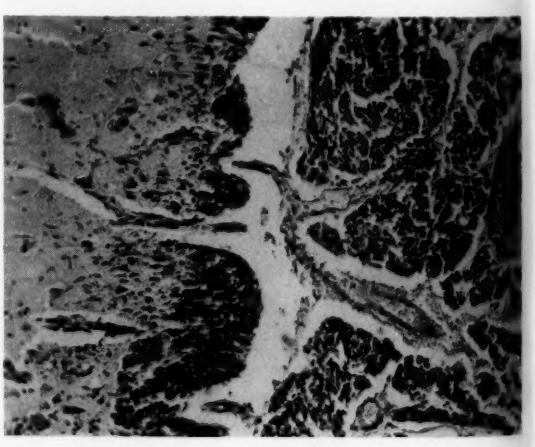

FIG. 8. Photomicrograph of left superior temporal gyrus showing both pia-arachnoid infiltration and actual invasion of the adjacent cerebral tissue. ×127.

throughout the pia-arachnoid space (Fig. 8). In these areas the tumor cells tended to show a pronounced spindle shape with very rare cells being rounded in appearance. Evidence of cellular and nuclear degenerative changes was present. The individual tumor nuclei were vesicular with many cells showing prominent nucleoli. The cells had scanty eosinophilic cytoplasm and the cell walls were indistinct. Numerous mitotic figures were present. Although pseudorosette formation was not convincing, in some areas delicate fibrillary cytoplasmic processes could be identified. These were stained according to the method of Rogers, Pappenheimer and Goetsch and silver positive fibrillary material could not be positively identified. There was marked extension of the tumor for varying degrees into the brain substance along the Virchow-Robin spaces. The sections taken from the spinal cord and cauda equina were of interest in that the tumor tended to be more uniform and round-cell in appearance (Fig. 9 and 10). The tumor cells in this area exhibited the same nuclear and cytoplasmic changes described above, but there was more evidence of tumor necrosis and hemorrhage. Pseudorosettes were not noted. Sections of the tumor from within the nasopharynx and also from the spinal cord were examined by Dr. Fred W. Stewart of Memorial Hospital, New York City, who diagnosed the tumor as a neuroblastoma.

Other significant microscopic findings were a lobular type bronchopneumonia and early lower nephron nephrosis.

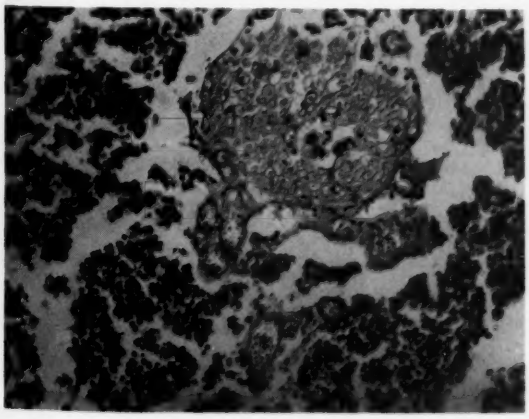

Fig. 9. Photomicrograph of tumor surrounding a nerve filament within the cauda equina. The round cell character of the tumor is prominent here. ×198.

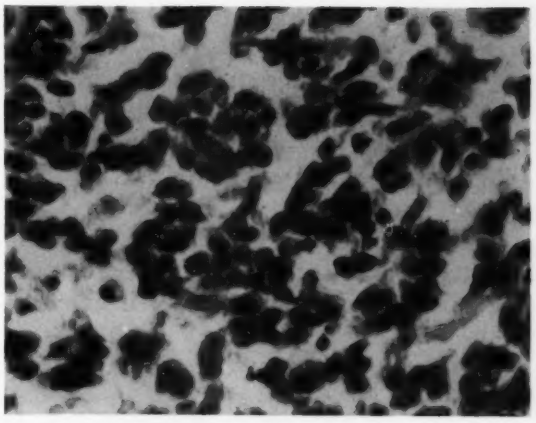

Fig. 10. High power magnification of an area of tumor from Figure 9. Note the range of nuclear variation and scanty amount of intercellular material. ×695.

DISCUSSION

Recognition of the fact that neuroblastoma may occur as a primary tumor in the nasal cavity is important. The inclusion of this type of tumor in the differential diagnosis of any tumor in the nasal cavity is necessary because of its unique biologic behavior. The characteristics include the extreme radiosensitivity of neuroblastomas generally and the tendency of this type of nerve tumor to metastasize by extruding cells into the cerebrospinal fluid, once it has invaded the cerebrospinal pathways.

The exact origin of these tumors is not completely understood, but in general it is accepted that they arise entirely independent from the central nervous system and probably within the olfactory mucous membrane. Various authors suggest that the origin may be from the olfactory placode, from the ganglion of Loci, which is a small organ situated at the anterior part of the olfactory placode, or conceivably from the vestigial Jacobson organ.[12] Berger, Luc and Richard[2] expressed the opinion that this tumor should be classified as a neuroblastoma, neuroepithelioma or neurocytoma, depending on whether its bulk is made up of stem cells, supporting cells or differentiated nerve cells.

In contradistinction to neuroblastomas

in other areas, the majority of these tumors have been reported in adults. There seems to be no great differential sex incidence. They present as a firm, reddened mass in the nasal cavity usually along the lateral wall. Some of them have been interpreted as being relatively benign, but they seem to spread rapidly and to invade the ethmoid cells and the orbit, causing a protuberance of the eye and partial or complete ophthalmoplegia.

As demonstrated by the course of this particular patient, they tend to be extremely radiosensitive locally and show the same propensity for metastasizing through the cerebrospinal fluid pathways as other neuroblastomas.

It is felt that the problems concerned in the microscopic differential diagnosis of this lesion deserve special mention for, as Allen[1] has pointed out, the esthesioneuroblastoma of the nasal passages is readily confused with the lymphomas, embryonal rhabdomyosarcomas, and with the anaplastic epidermoid carcinomas. According to Eggston and Wolff[6] the nasopharyngeal lymphosarcomas may occur as the small round cell lymphoblastic type, the large round reticulum cell sarcoma or as an undifferentiated type which simulates epithelial cells. The first variant is characterized by cells that are small and round and which have typical lymphocytic characteristics. They do contain numerous nucleoli and mitotic figures but do not form follicles or take on the histologic architecture of a lymph node. Infiltration of adjacent structures is rather prominent. The reticulum cell lymphosarcomas are highly malignant tumors and grow more rapidly than the pure lymphocytic type. Histologically, they occur as a diffuse cellular mass of large round cells with intercellular fibrillae. The nuclear chromatin is vesiculated and numerous prominent nucleoli are present. The undifferentiated variant described by Eggston and Wolff seems to be a transitional cell tumor characterized by large, round, vesicular nucleated cells, the protoplasm of which is poorly outlined and is arranged as a syncitial type tissue. Lymphocytes are scattered throughout the tumor cells and one infers from the illustrations that this is the same tumor generally known as the lymphoepithelioma.

It must be emphasized that the tumors which presumably arise in nasopharyngeal lymphoid tissue—*i.e.*, the lymphoepitheliomas and the transitional cell carcinomas—can readily be confused with the esthesioneuroblastoma. It will be remembered that the case herein reported was originally considered to be a transitional cell carcinoma on the basis of the biopsy from the ethmoid area. Cappell[4] separates this group of tumors into 3 types; the lymphoepithelioma of Regaud, the lymphoepithelioma of Schmincke, and the transitional cell carcinoma. According to Cappell, the Regaud variety is made up of strands of epithelial cells with large pale-staining vesicular nuclei, poorly delimited cytoplasm and embedded in a stroma rich in lymphocytes. The Schmincke tumor is composed of irregular anastomosing trabeculae of ill-defined cells with large vesicular nuclei. In many places the appearance of the epithelial columns may be lost and the cells become dissociated from one another giving rise to a loosely packed mass of round, oval or polygonal cells. In some parts they are separated by a dense lymphocytic infiltration which tends to isolate them from one another and renders recognition of the individual cells difficult. The transitional cell carcinoma is distinguished from the other two members of this group by the fact that it takes origin from the surface epithelium and also because the tumor cells form broad alveoli in which central necrosis and degeneration are more common than in the Regaud or Schmincke types. There are no keratinized cells and the tumor is devoid of intercellular bridges. The epithelial cells may be embedded in fibrous stroma or a stroma rich in lymphocytes, but there is an absence of the intimate mixture of lymphocytes throughout the epithelial alveoli as in the Regaud and Schmincke tumors.

Finally, the possibility of embryonal rhabdomyosarcoma, as Allen points out,

must be considered in the differential diagnosis of the esthesioneuroblastoma. Embryonal rhabdomyosarcoma most commonly takes origin in the orbital, facial, and cervical musculature and may present a microscopic picture quite similar to the tumor described herein. Stobbe and Dargeon[13] have stated that while the microscopic characteristics of the embryonal rhabdomyosarcoma differ somewhat in various regions, the predominant cell is the short spindle cell with an oxyphilic homogeneous or granular cytoplasm. The cells are arranged as parallel, anastomosing, or interlacing bands. Round cells of various types are associated with the spindle cells and giant cells are rarely encountered. Longitudinal fibrils may be present in the spindle-shaped cells and cross striations are found with difficulty. The variation in cell type that characterizes these tumors and their superficial resemblance in growth pattern to fibrosarcoma should help to separate them from neuroblastoma on a histologic basis.

SUMMARY

Primary neuroblastomata originating in the olfactory mucous membrane are relatively rare but do occur and should be included in the differential diagnosis of any tumor originating in this region. Their course may seem rather benign but in many instances they rapidly invade the ethmoid labyrinth and the orbit with subsequent exophthalmos and ophthalmoplegia. They tend to be extremely radiosensitive and may metastasize by extruding cells into the cerebrospinal fluid.

Paul A. Riemenschneider, M.D.
Syracuse Memorial Hospital
736 Irving Avenue
Syracuse 10, New York

REFERENCES

1. Allen, A. A. Tissue collection prepared at Memorial Hospital for Cancer and Allied Diseases under grant from The National Cancer Institute, Division of Laboratories and Research, New York State Department of Health, Case #509, 1951, Vol. 5.
2. Berger, L., Luc, and Richard. L'esthésioneuroépitheliome olfactif. *Bull. de l'Assoc. franç. p. l'étude du cancer*, 1924, *13*, 410.
3. Berger, L., and Coutard, H., II. L'esthésioneurocytome olfactif. *Bull. de l'Assoc. franç. p. l'étude du cancer*, 1926, *15*, 404–414.
4. Cappell, D. F. Pathology of nasopharyngeal tumors. *J. Laryng. & Otol.*, 1938, *53*, 558–580.
5. da Costa, C. A. Olfactory neuroepithelioma: Histologic study of case. *Lisboa méd.*, 1946, *23*, 99.
6. Eggston, A. A., and Wolff, D. Histopathology of the Ear, Nose and Throat. Williams and Wilkins Company, Baltimore, 1947, p. 292.
7. Eigler, G. Unusual tumor of nose. *Hals-Nasen u. Ohrenarzt*, 1947, *28*, 320.
8. Jemmi, C. I tumori neurogeni del naso (gliomi e neuroblastomi). *Oto-rino-laring. ital.*, 1947, *15*, 149–183.
9. Martin, J. F., Dargent, M., and Gignoux, M. Les tumeurs nerveuses des fosses nasales. *Ann. d'otolaryng.*, 1949, *66*, 253–266.
10. Portmann, G., and Beillard, P. J. Les tumeurs des fosses nasales. *Rev. Oto.-Rhinolaryng.*, 1947, *68*, 1 and 125.
11. Portmann, M. M., Bonnard, and Moreau. Sur un cas de tumeur nerveuse des fosses nasales (esthésioneuroblastome). *Acta otolaryng.*, 1929, *13*, 52.
12. Schall, L. A., and Lineback, M. Primary intranasal neuroblastoma; report of 3 cases. *Ann. Otol., Rhinol. & Laryng.*, 1951, *60*, 221–229.
13. Stobbe, D., and Dargeon, H. W. Embryonal rhabdomyosarcoma of head and neck in children and adolescents. *Cancer*, 1950, *3*, 826–836.
14. Tavares, A. Nervous tumors of nasal fossae. *Portugal Med.*, 1941, No. 8, 305–316.
15. Wohlwill, F. Contribuições morfológicas para o problema dos tumores; trés formas differentes de neoplasias radio-sensiveis; tumores embrionários do tecido nervosa. *Lisboa méd.*, 1936, *13*, 489–519.

CARCINOMA OF THE NASAL FOSSA*

By ROBERT G. PARKER, M.D.
SEATTLE, WASHINGTON

CARCINOMA of the nasal fossa is usually classified with carcinoma of the paranasal sinuses[3,4,5,6,9,10,11,14] and in some instances with carcinoma of the nasopharynx.[7,12] Although a separation of these entities has been reported infrequently in the literature,[1,2,8] such a separation is necessary for assessment of treatment and results. In many instances, a sharp distinction cannot be made, especially when there is evidence of destruction of the intervening wall between the maxillary sinus and the nasal fossa, with tumor in both locations, and when there is similar simultaneous involvement of the ethmoid sinuses and the superior portion of the nasal fossa. Nevertheless, such a distinction frequently is possible. For the purposes of this discussion, only cases involving the nasal fossa, which are not questionable in the above stated sense, will be considered.

MATERIAL

Between 1940 and 1954, 14 cases of carcinoma of the nasal fossa have been seen at the Tumor Institute of the Swedish Hospital, Seattle, Washington. Following initial review of these cases and those of carcinoma of the paranasal sinuses, it became apparent that the prognosis of the two entities was so different that separation was desirable. In our initial study of 20 cases of carcinoma of the nasal fossa, each of which had been diagnosed by biopsy, there were only 2 deaths due to tumor. This prompted a review of the histology, and in so doing, in 6 cases previously designated as epidermoid carcinoma, Grade 1, the diagnosis was changed to squamous cell papilloma. In 4 of these 6 cases, the original microscopic examination had been made by the same pathologist years before.

CLINICAL FINDINGS

The most frequent presenting complaint was that of a mass in the nasal fossa. In 4 of 6 instances, this mass had been noted by the patient for two or more years. Epistaxis, which was present in 4 cases, usually was of lesser duration, although in one instance, this complaint dated four years. Likewise nasal obstruction was of lesser duration, except in one patient who had had this complaint for eighteen months. Of the original 20 cases, only one had had pain and that patient later proved to have a squamous cell papilloma. Otherwise, the same clinical findings were present in those with carcinoma and those with the altered diagnosis of squamous cell papilloma.

In the descriptions of the lesions by the original examiners, the term "irregular mass" or "nodule" was used eight times, "papillary" or "polypoid" four times, "ulceration" three times, "induration" two times and "granularity" once. As regards the site of origin and size of the lesion when first seen, in 6 instances the tumor was limited to the septum; in 5 it filled the fossa; twice the tumor extended into the nasopharynx, in both instances after filling the fossa; once the lateral wall only was involved; once the floor of the fossa only; and once both the floor of the fossa and the base of the septum were involved. Thus, it appears that in this small group of cases, the most frequent site of origin was the mucosa of the nasal septum, although in previous reports it has been stated that this is a rare site of origin.[1,13] In those lesions which proved to be squamous cell papillomas, the same descriptions were used. In 3 of the 6 cases the tumor filled the nasal fossa, while in 2 instances the lesions were limited to the nasal septum.

* From the Tumor Institute of the Swedish Hospital, Seattle, Washington.

Fig. 1. Case 1. Moderately well-differentiated squamous cell carcinoma probably arising from lower septum and filling nasal fossa anteriorly.

MICROSCOPIC FINDINGS

Of the 14 substantiated cases, 3 had well-differentiated, 4 moderately well-differentiated and 5 undifferentiated carcinomas. One had a malignant mixed tumor and 1 had a basal cell carcinoma, although grossly this lesion was entirely within the mucocutaneous junction on the anterior floor of the fossa. One undifferentiated carcinoma and the mixed tumor had originally been called schneiderian carcinoma. There were no cases of adenocarcinoma. Between 1940 and 1957, other tumors of the nasal fossa seen at the Tumor Institute were diagnosed microscopically as squamous cell papilloma in 7 additional cases, as melanoma in 2 cases, as hemangioma in 2 cases, and as plasmacytoma, sarcoma, fibroma and chondroma in 1 case each.

Fig. 2. Case 1. (*A*) Height of most severe skin reaction following 4,350 r (skin) in eighteen days with 200 kv. roentgen therapy. (*B*) Appearance of skin one month later.

Fig. 3. Case VII. Epidermoid carcinoma Grade III, involving anteroinferior septum and adjacent floor of nasal fossa.

DIAGNOSIS

The diagnosis, unless there is involvement of the maxillary or ethmoid sinuses, is relatively easy. This tumor should readily be discovered by careful examination. In the initial evaluation careful study of roentgenograms of the paranasal sinuses is important. The positive roentgen findings in our series were thickening of the mucosa and/or diffuse cloudiness of the adjacent maxillary sinus. In no instance was there evidence of bone destruction. In those cases in which the malignant neoplasm involves the lateral wall of the nasal fossa and the adjacent maxillary sinus has an abnormal appearance roentgenographically, surgical exploration of the antrum is considered to be indicated.

METASTASES

Discernible metastases in carcinoma of the nasal fossa do not occur early.[1] Only 2 of our patients developed metastases during their period of observation of two and one-half and ten years, respectively. Dissemination was both by the lymphatic and hematogenous route.

Fig. 4. Case X. Appearance of skin five years after administration of 5,000 r (skin) in thirty-seven days with 250 kv. roentgen therapy.

Fig. 5. Appearance of skin five and one-half years after administration of 6,000 r (skin) with 800 kv. and 400 kv. roentgen therapy.

Fig. 6. Case xii. (*A*) Exit reaction with 6,300 r (max.) in twenty-five days with 2 mev. roentgen therapy. (*B*) Illustrating regrowth of normal appearing hair in two months.

Fig. 7. (*A*) Lesion treated as a squamous cell carcinoma. Diagnosis changed to squamous papilloma. (*B*) Three months after treatment with 200 kv. roentgen therapy to dose of 4,900 r (skin) in nineteen days.

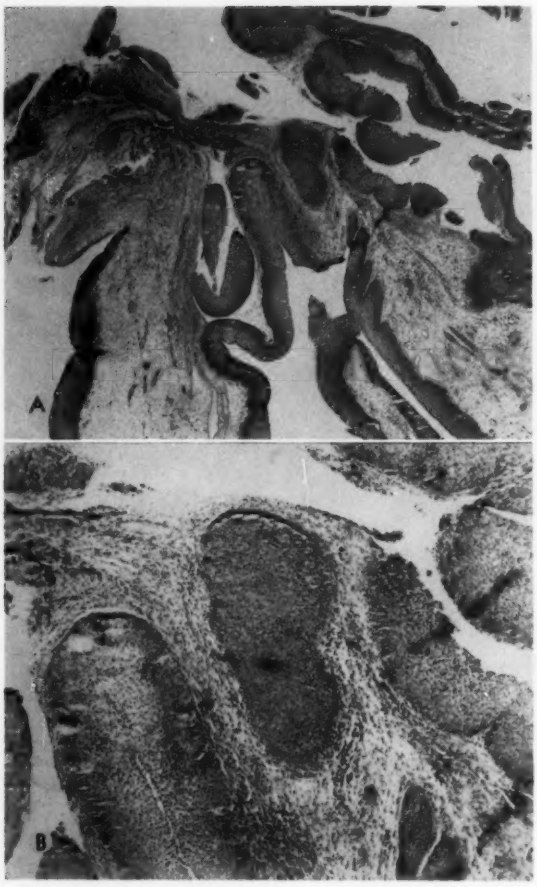

FIG. 8. (*A*) Magnification 10× of papillary lesion filling left nasal fossa and protruding into nasopharynx. Originally diagnosed and treated as a Grade 1 carcinoma. (*B*) Magnification 90×.

ROENTGEN THERAPY

Roentgen therapy was the initial method of treatment in 12 of the 14 cases of carcinoma and in the 6 re-diagnosed cases of squamous cell papilloma. Two patients with small well-differentiated lesions on the septum were referred for surgery as the initial method of treatment.

The details of treatment in each case are given in Table 1. It has been stated that it is difficult to treat nasal fossa malignant lesions with external roentgen therapy alone.[4] In most cases, we believe external roentgen therapy to be the preferred method.

Treatment reactions have varied widely, ranging from minimal erythematous mucosal and cutaneous reactions to moderately severe desquamative and membranous reactions. All have healed without serious sequelae. The most bothersome complaint has been persistent dryness and crusting of the mucosa. Symptomatic control has been obtained with use of bland lubricating agents. Patients are more tolerant of these discomforting sequelae if they understand the alternative surgical treatment with the associated period of hospitalization and the frequently resulting anatomic deformity. Consequently, in the initial evaluation it is advantageous to have an estimate of the extent of the surgical resection which would have to be performed.

RESULTS

Of the 12 patients with carcinoma initially treated with roentgen therapy, 2 died with metastases. One of these had a metastatic lesion in the soft tissue of the thigh when first seen. He received roentgen therapy for control of hemorrhage from the nasal fossa. At the time of death, three months later, there were widespread metastases, including pulmonary lesions. The primary lesion was not controlled. The second patient died with uncontrolled homolateral cervical lymph node metastases, twelve months after treatment of the primary lesion, a moderately well-differentiated carcinoma involving the lower septum and floor of the fossa and filling the anterior fossa. This primary lesion remained controlled until death. In 2 cases there was local recurrence treated by minimal resection. A fourteen year old female initially seen with extensive disease involving the entire fossa was reported as having schneiderian carcinoma. On evaluation at that time, it was estimated that resection, if possible, would have been mutilating. Thus roentgen therapy was attempted. There was no clinical evidence of tumor until six and one-half years later, at which time, a small nodule was noted on the left posterosuperior aspect of the septum. This was the last site from which the tumor disappeared following roentgen therapy through an anterior field. Biopsy was positive. The tumor

TABLE I

CARCINOMA OF THE NASAL FOSSA TREATED WITH EXTERNAL ROENTGEN THERAPY

Case No.	Patient Age, Sex	History	Gross Lesion	Histology	Treatment	Result
I	52 yr. old white male 1940	Mass in left nasal fossa for 2 mo.	Probably arising from lower septum and floor of fossa. Filling entire fossa anteriorly and extending posteriorly for 2 cm. Superficial ulceration	Squamous cell carcinoma, moderately well-differentiated	200 kv. *Field:* Left lateral nasal, 4 cm. diameter circle *Dose:* 4,350 r (skin) in 18 da.	Rapid regression of tumor so that not detectable at end of treatment. Left submaxillary lymph adenopathy noted elsewhere in 4 mo. Treated elsewhere by local excision and roentgen therapy. Died of uncontrolled disease in neck 12 mo. after treatment
II	66 yr. old white male 1943	Mass in right nasal fossa for 2 yr.	Papillary growth, 2 cm. in diameter, on inferior right septum. Superficial ulceration	Squamous cell carcinoma. Grade 1	200 kv. *Field:* Right lateral nasal, 4×4 cm. *Dose:* 4,250 r (skin) in 16 da.	Rapid tumor response and not detectable shortly after treatment. Well without tumor 8 yr. (1951). Minimal mucosal atrophy
III	57 yr. old white female 1945	Partial obstruction of right nasal fossa for 18 mo.	Grayish-red nodule in right nasal fossa, 3 cm. within mucocutaneous junction. Site of origin not determined	Undifferentiated carcinoma (schneiderian)	800 kv. *Field:* Right anterior nasal, 2.5×2.5 cm. *Dose:* 5,200 r (max.) in 26 da.	Visible regression of tumor by 2,200 r in 10 da. and disappearance shortly after treatment. Tumor free 6 yr. later. Slight atrophy and dryness of nasal mucosa
IV	70 yr. old white male 1947	Mass on left nasal septum for several years	Flat, indurated 1 cm. tumor on mucosa of left nasal septum extending to mucocutaneous junction. Central ulceration	Squamous cell carcinoma, moderately well-differentiated	120 kv. *Field:* Left anterior nasal, 1.5 cm. diameter circle *Dose:* 3,750 r (skin) in 6 da.	Tumor disappeared by 6 wk. Tumor free 10 yr. after treatment. Mild mucosal atrophy
V	45 yr. old white male 1949	Nasal polyps removed from left fossa 7 times in previous 6 yr. Polyps removed 1 yr. before proved to be carcinoma on review of material	Complete obstruction of left nasal fossa. Necrosis in posterior fossa at site of recent resection of polyp. Large, firm polypoid growth protruding posteriorly from left fossa. Mass posteriorly measuring 1.5 cm. in diameter and bulging into left nasopharynx. Right fossa encroached upon posteriorly by growth from left fossa	Undifferentiated epidermoid carcinoma in a polyp	800 kv. *Fields:* 1. Anterior nasal, 5×5 cm., 5,000 r (max.) in 49 da. 2. Left lateral nasopharynx, 6×7 cm., 3,300 r (max) in 49 da. 3. Right lateral nasopharynx, 6×7 cm., 3,000 r (max.) in 49 da. *Dose:* Calculated at 8 cm. in midsagittal plane at junction of 3 fields with allowance for bone absorption: 5,650 r in 49 da. 4. Additional radium in nasopharynx with small Manchester ovoid: 1,000 r_a on surface every other day for 3 times applied 6 wk. after roentgen therapy	Membranous reaction over tumor by 6 wk. Tumor reduced to 1 cm. nodule in posterior fossa before radium application 6 wk. after roentgen therapy. Nodule disappeared 1 wk. after last radium application. No tumor 6½ yr. after treatment. Moderate crusting and bleeding from mucosa of left nasal fossa
VI	14 yr. old white female 1950	Malignant polyps removed from left nasal fossa 1 yr. before. Four year history of left epistaxis and left frontal headache	Grayish, firm tissue occluding posterior left fossa, arising posteriorly and attaching to septum	Initially called schneiderian carcinoma. Later called mixed tumor of mucous membrane. Same histology 6½ yr. later	200 kv. *Field:* Direct anterior nasal, 3×4 cm. *Dose:* 5,150 r (skin) in 31 da.	Considerable tumor reduction after 2,300 r (skin) in 14 da. Last detectable tumor disappeared from superior posterior septum after 4 mo. Clinically tumor free for 6½ yr. 1 cm. nodule reappeared within treatment field at site where last disappeared from superior posterior septum. Resection of mucosa, cartilage and perpendicular plate of ethmoid. No evidence of tumor 14 mo. after resection

Continued on following page.

TABLE I (*continued*)

Case No.	Patient Age, Sex	History	Gross Lesion	Histology	Treatment	Result
VII	69 yr. old white male 1950	Non-healing "sore" left nostril for 3 yr.	0.5 cm. ulceration of mucosa of anteroinferior left septum. Induration along floor and lower septum for 1.0 cm.	Epidermoid carcinoma, Grade III	140 kv. *Field:* Anterior nasal, 2.5 cm. diameter circle *Dose:* 4,550 r (skin) in 22 da.	Tumor disappeared by 8 wk. Died of heart disease 30 mo. after treatment. No evidence of tumor
VIII	65 yr. old white male 1950	Abnormal left nasal discharge and epistaxis for 9 mo. Mass on anterior right thigh for 5 mo.	Tumor filling left nasal fossa. Mass, 12×8×20 cm. in soft tissue of anterior right thigh	Nose: Undifferentiated carcinoma Thigh: Same	800 kv. *Fields:* 1. Anterior nasal, 5×7 cm., 4,800 r (max.) in 22 da. 2. Right lateral nasopharynx, 6×7 cm., 3,000 r (max) in 34 da. 3. Left lateral nasopharynx, 6×7 cm., 3,000 r (max) in 34 da. *Dose:* 8 cm. deep in sagittal plane at junction of 3 fields; 6,660 r in 56 da.	Nasal fossa tumor not controlled. Relief of obstruction and hemorrhage. Died with widespread metastases, including pulmonary, 3 mo. after treatment
IX	77 yr. old white female 1952	Swelling in left nasal fossa with complete obstruction for 2 mo.	Granular tumor completely occluding left nasal fossa, extending to within 1 cm. of mucocutaneous junction	Undifferentiated carcinoma (transitional Grade III)	800 kv. and 400 kv. *Field:* Anterior nasal, 5×5 cm. *Dose:* 6,050 (max.) in 31 da.	Some reduction of tumor with 1,400 r in 7 da. Tumor not detectable 2 wk. after treatment. Recurrent nodule on middle turbinate 10 mo. later removed by snare and base cauterized. No tumor 4½ yr. after resection
X	66 yr. old white female 1953	Discharge of tissue and epistaxis for 3 mo.	Papillary tumor arising in region of right inferior turbinate	Papillary carcinoma, well-differentiated	250 kv. *Field:* Anterior nasal, 2×5 cm. *Dose:* 5,000 r (skin) in 37 da.	Tumor disappeared by 2 wk. after treatment. No tumor 4½ yr. later
XI	53 yr. old white male 1953	Nodule in nose for 3 yr.	0.6 cm. nodule with central ulceration on floor of left nasal fossa just inside mucocutaneous junction	Basal cell carcinoma	120 kv. *Field:* Anterior nasal, 1.5 cm. diameter circle *Dose:* 4,200 r (skin) in 9 da.	Tumor disappeared within few weeks. No tumor in fossa at time of death, 32 mo. later. Cause of death was carcinoma of bronchus
XII	58 yr. old white male 1954	"Stuffiness of left nose" for 8 mo.	Papillary tumor covering lower one inch of anterior nasal septum, stopping at mucocutaneous junction	Undifferentiated carcinoma	2 mev *Field:* Anterior nasal, 3×4 cm. *Dose:* 6,300 r (max.) in 25 da.	Tumor gone by 8 wk. No evidence of tumor 3¾ yr. later

Treatment Factors:
120 kv.; 3 ma.; 16 cm. FSD; filter: 3 mm. Al
200 kv.; 20 ma.; 60 cm. FSD; filter: 2 mm. Cu+1 mm. Al; HVL = 1.3 mm. Cu
250 kv.; 15 ma.; 50 cm. FSD; filter: Thoraeus II; HVL = 1.8 mm. Cu
800 kv.; 10 ma.; 100 cm. FSD; filter: inherent+4.5 mm. Pb+2 mm. Al
+0.8 mm. Sn+0.26 mm. Cu+1 mm. Al
+3 mm. celluloid; HVL = 3 mm. Pb or 9.1 mm Cu
2 mev.; 100 μa.; 100 cm. FSD; filter: inherent; HVL = 12.1 mm. Cu

was of identical histologic appearance as noted six and one-half years before, although the diagnosis was changed to mixed tumor. The involved portion of the septum was liberally resected. The patient is without evidence of tumor fourteen months after resection and ninety-three months after the initial diagnosis. The other case of persisting tumor following roentgen therapy was that of a seventy-seven year old female with a transitional cell or undifferentiated carcinoma completely occluding the left nasal fossa. Ten months after roentgen therapy, a small nodule on the middle turbinate was removed by snare and cautery of the base. This patient has remained without clinical evidence of tumor for four and one-half years after resection or nearly five and one-half years after diagnosis. Of the remaining 8 cases, one, a sixty-nine year old male, died of heart disease thirty months after treatment. There was no evidence of residual tumor in the nasal fossa at that time. Another, a fifty-three year old male, died with a second primary malignant neoplasm of the bronchus, thirty-two months after treatment of his nasal fossa carcinoma. At autopsy, there was no evidence of residual disease in the nasal fossa. Of the remaining 6 cases, which have been followed for periods between three and one-half and ten years, none has had clinical evidence of tumor.

In reviewing the 6 cases treated as nasal fossa carcinoma but later re-diagnosed squamous cell papilloma, it can be stated that such treatment was effective although in retrospect unduly vigorous. All were tumor-free four to eight and one-half years after treatment. As an example, a thirty-six year old white female was first seen with a four year history of progressive obstruction of the left nasal fossa. Obstruction had been complete for two years. A firm, granular mass filled the fossa from 1 cm. inside the mucocutaneous junction extending through the posterior choana to protrude into the nasopharynx. Treatment consisted of 2 mev. roentgen therapy, which was directed through a direct anterior nasal field and opposing lateral nasopharyngeal fields. The dose 8.5 cm. deep in the sagittal plane at the junction of the three fields was 6,000 r in sixty days. This patient has been tumor free and without sequelae for four and one-half years.

SUMMARY

In carcinoma of the nasal fossa judicious external roentgen therapy is not only feasbile but is a desirable method of treatment. In lesions of the anterior fossa, low or medium voltage roentgen therapy appears preferable. In posterior fossa lesions, especially with extension into the nasopharynx, the use of supervoltage roentgen therapy is more advantageous. Minor sequelae are common, but no detectable complications were observed involving underlying cartilage or bone. Obvious involvement of cartilage or bone prior to treatment is a contraindication to roentgen therapy. In view of the favorable results of treatment of malignant neoplasms of the nasal fossa with roentgen therapy, separation of these lesions from those arising in the paranasal sinuses is important for adequate evaluation of both entities.

1211 Marion Street
Seattle 4, Washington

REFERENCES

1. Ackerman, L. V., and del Regato, J. A. Cancer: Diagnosis, Treatment, and Prognosis. Second edition. C. V. Mosby Co., St. Louis, 1954, pp. 198–212.
2. Cade, S. Malignant Disease and Its Treatment by Radium. Volume II. Second edition. Williams & Wilkins Company, Baltimore, 1949, pp. 184–197.
3. Capps, F. C. W., and Williams, I. G. Discussion on malignant diseases of nasal cavity and sinuses. *Proc. Roy. Soc. Med.*, 1950, *43*, 665–674.
4. Devine, K. D., Scanlon, P. W., and Figi, F. A. Malignant tumors of nose and paranasal sinuses. *J.A.M.A.*, 1957, *163*, 617–621.
5. Geschickter, C. F. Tumors of nasal and paranasal cavities. *Am. J. Cancer*, 1935, *24*, 637–660.
6. Larsson, L. G., and Mårtensson, G. Carcinoma of paranasal sinuses and nasal cavities; clinical study of 379 cases treated at Radiumhemmet and Otolaryngologic Department of

Karolinska Sjukhuset. *Acta radiol.*, 1954, *42*, 149–172.

7. Lenz, M. Symposium: Malignant tumors; malignant neoplasms of nose, nasopharynx and paranasal sinuses: Evaluation of radiation therapy. *Tr. Am. Acad. Ophth.*, 1951, *55*, 214–225.
8. MacComb, W. S., and Martin, H. E. Cancer of nasal cavity. Am. J. Roentgenol. & Rad. Therapy, 1942, *47*, 11–23.
9. Ohngren, L. G. Malignant tumors of maxilloethmoidal region. Clinical study with special reference to treatment with electrosurgery and irradiation. *Acta oto-laryng.*, 1933, Suppl. 19, 1–476.
10. Schall, L. A. Cancer of nose and nasal sinuses. *Laryngoscope*, 1943, *53*, 240–245.
11. Schall, L. A. Malignant tumors of nose and nasal accessory sinuses. *J.A.M.A.*, 1948, *137*, 1273–1276.
12. Schall, L. A. Symposium: Malignant tumors; malignant neoplasms of nose, paranasal sinuses and nasopharynx: Evaluation of surgical treatment. *Tr. Am. Acad. Ophth.*, 1951, *55*, 209–213.
13. Sooy, F. A. Primary tumors of nasal septum. *Laryngoscope*, 1950, *60*, 964–992.
14. Willie, C. Malignant tumors in nose and its accessory sinuses. *Acta oto-laryng.*, 1947, Suppl. 65, 1–58.

VOL. 80, NO. 5

RADIATION THERAPY FOR CANCER OF THE TONSIL*

By GLENN E. SHELINE, M.D., MALCOLM D. JONES, M.D., *and* LEWIS F. MORRISON, M.D.†
SAN FRANCISCO, CALIFORNIA

RADIATION therapy has become the main treatment of malignant lesions of the tonsil. Over the years, widely varying forms of radiation therapy have been used. At times, interstital therapy with radium or radon has enjoyed a period of popularity. External radiation utilizing lead grids has been tried. Most radiation therapy has been given with a quality of beam in the range of 200 kv.; however, there is evidence to suggest that supervoltage radiation may give improved results.[2] While present therapy yields a very significant salvage, both in terms of eradication and palliation, it still leaves much to be desired. In an effort to evaluate radiation therapy as used at the University of California Hospitals, all cases with malignant lesions of the tonsil seen since 1931 have been reviewed. The results of this review are presented here.

MATERIAL

A total of 82 patients with malignant lesions of the tonsil were treated between 1931 and June 30, 1956. Of these, 16 were female and 66 were male, a ratio of 1:4. The average age for the female patients was sixty years; the average for males was fifty-eight years. While this is primarily a disease of the sixth and seventh decades, 18 of our patients were in the fourth or fifth decade. The youngest patient was thirty-three years of age. There was no evident correlation in our data between incidence of the disease and race, occupation, or habits.

The average interval between onset of symptoms and the beginning of radiation therapy was seven months. In a number of patients, this interval was long because of previous therapy of some type. Ten of the 82 patients had had either unilateral or bilateral tonsillectomy. Another 10 had had some form of systemic or topical antibiotic therapy which resulted in delays of up to twenty-one months. One tonsil had been cauterized. Fifty-two of the patients had had no previous therapy for the tonsillar lesion.

Nine patients of the total 82 had had previous radiation therapy and must be classified as retreatments. Two of these had had interstitial radium therapy: 1 had had interstitial radium plus a radical neck dissection; and 6 had had roentgen therapy. All 9 had local recurrence of lymph node metastases at the time of referral.

The most frequent presenting symptom was sore throat; this occurred in 41 patients. Five had pain referable to the tongue or jaw. In 20, the chief complaint was of a mass in the neck; 12 complained of a mass in the throat; 8 had dysphagia, and 15, weight loss. In 14, there were symptoms referable to the ear (earache, tinnitus, altered hearing). Gross bleeding was present in 5 patients.

The histologic diagnoses are shown in Table 1. The distribution of cases among the various histologic groups is closely similar to a previously reported series.[1] The 7 cases without biopsy had strong clinical evidence of a malignant lesion arising in the tonsil; 5 subsequently expired of metastases from the tonsillar lesion.

The primary lesion was in the right tonsil in 43 cases, in the left tonsil in 36, and involved both tonsils in 3. Sixty-one per cent of the patients had palpably en-

* From the Department of Radiology and the Sub-department of Otorhinolaryngology, University of California School of Medicine, San Francisco, California.
† Deceased.

TABLE I

HISTOLOGIC DIAGNOSES

Squamous cell carcinoma	48
Transitional cell carcinoma	11
Lymphoepithelioma	2
Undifferentiated carcinoma	7
Unclassified	3
Lymphosarcoma	3
Adenocarcinoma	1
No biopsy performed	7

larged cervical lymph nodes at the time of the initial visit. In 10 per cent, the lymph node involvement was bilateral. Of the 32 patients having no metastases at the time of the initial visit, 4 subsequently developed cervical metastases. The metastases, when present, usually involved the cervical lymph nodes on the same side as the primary lesion; however, in 2 cases, only contralateral cervical lymph node involvement was evident. Although metastases were usually limited to the neck area, they did occur once in the thoracic wall and in the liver, and three times in the lung.

TECHNIQUE AND RESULTS

The primary approach has been the use of roentgen therapy administered either through external fields or through a combination of external fields and intraoral cones. The quality of roentgen rays used has varied depending upon the machines available. Of the 82 patients, 23 were treated with roentgen rays having a half-value layer of 9 mm. Cu. With this quality of radiation, only external fields were used. An additional 56 patients were treated with roentgen rays having a half-value layer between 4.5 and 0.5 mm. Cu; the latter quality was used for intraoral cone therapy. Of the 56 patients, 23 were treated with external roentgen rays only: 15 with roentgen rays of approximately 1.1 mm. Cu half-value layer; 5 with roentgen rays of approximately 2.4 mm. Cu half-value layer; and 3 with roentgen rays of approximately 4.5 mm. Cu half-value layer. Twenty-three more received intraoral cone therapy; 13 of these were treated with external fields, as well. The other 10 patients, of the 56 treated with roentgen rays, received only grid therapy.

The remaining 3 of the 82 patients considered were treated with radon seed therapy.

Results. The survival data are presented in Tables II, III, and IV. In Table II, the over-all survival for the 82 cases is given. It is seen that 56 out of 82 have been at risk for five years and 39 for ten years, the over-all survival being 20 per cent and 13 per cent respectively. It should be emphasized that these are gross survival rates, with no correction made for those who died of unrelated disease, or for age at time of treatment. Table III gives five and ten year survival rates of 13 and 12 per cent for patients treated only by external roentgen therapy. The survival in this group is somewhat less than the average survival for all methods of therapy, but this probably reflects the fact that many of the more advanced cases fell into this group and received therapy for palliation alone. Table IV shows the survival data for patients treated by intraoral cone and external roentgen therapy; these data are undoubtedly improved by the fact that only the smaller lesions were selected for intraoral cone therapy.

Of the 56 patients at risk for five years, 45 had expired. The average survival of this group from the time of therapy was seventeen months. All but 4 of the deaths were within thirty-six months; 3 of the 4 probably died from unrelated disease. The five year survival in those without clinically evident metastases at the time of the initial visit was 33 per cent (8 of 24), while the five year survival in those with metastases was 9 per cent (3 of 32).

Treatment Methods. There was insufficient standardization of treatment to permit evaluation of survival as a function of the method of treatment employed. The largest group of patients (35) was treated with either opposing lateral fields or multi-

TABLE II

SURVIVAL IN ALL CASES OF MALIGNANT LESIONS OF THE TONSIL

Year of Initial Treatment at University of California Hospitals	New Cases	Number of Years after Radiation Therapy									
		1	2	3	4	5	6	7	8	9	10
1931	2	2	1	1	1	1	1	1	1	1	1
1932	3	3	2	1	1	1	1	1	1	1	1
1933	2	2	2	2	2	0	0	0	0	0	0
1934	5	3	2	1	0	0	0	0	0	0	0
1935	0	0	0	0	0	0	0	0	0	0	0
1936	4	1	0	0	0	0	0	0	0	0	0
1937	2	2	2	0	0	0	0	0	0	0	0
1938	4	4	2	2	2	1	1	1	1	1	1
1939	3	1	0	0	0	0	0	0	0	0	0
1940	3	3	2	1	1	1	1	1	1	1	1
1941	1	0	0	0	0	0	0	0	0	0	0
1942	4	3	0	0	0	0	0	0	0	0	0
1943	3	1	1	1	1	1	1	1	1	1	1
1944	2	0	0	0	0	0	0	0	0	0	0
1945	1	1	1	0	0	0	0	0	0	0	0
1946	3	3	3	3	3	3	2	2	2	0	
1947	6	4	4	2	2	2	2	1	1		
1948	6	3	3	2	2	1	0	0			
1949	1	0	0	0	0	0	0				
1950	1	1	0	0	0	0					
1951	5	4	3	3	2						
1952	6	3	3	2							
1953	3	3	3								
1954	5	4									
1955	4										
1956	3										
Cases at Risk	82	75	70	67	61	56	55	54	48	42	39
Number Surviving		51	34	21	17	11	9	8	8	5	5
Per Cent Surviving		68	49	31	28	20	16	15	17	12	13

ple fields. Twenty patients were treated through single lateral fields; of these, 10 were treated through lead grids. Thirteen patients were treated using an intraoral cone plus unilateral or bilateral external fields. The remaining patients form a heterogeneous group treated with interstitial radium, external grid fields plus radon, or open external fields plus interstitial radium or radon. Grid therapy was first used at this institution in 1951; hence, none of these patients was considered in the five year survival figures.

Field Size. When external fields were used, they were generally of a size to encompass the primary lesion plus the "tonsillar" lymph node. If other lymph nodes were palpable in the neck, the ipsilateral field size was increased to include the cervical lymph nodes. The contralateral field, when used, varied in size from that only sufficient to cover the primary cancer to that large enough to include the entire cervical chain. When intraoral cone therapy was employed, the cone was 3 cm. in diameter.

Twelve patients with relatively small lesions were treated through fields measuring 49 sq. cm. or smaller. Two of these patients have survived without evidence

TABLE III

SURVIVAL IN CASES OF MALIGNANT LESIONS OF TONSIL TREATED BY EXTERNAL ROENTGEN THERAPY ONLY

Year of Initial Treatment at University of California Hospitals	New Cases	Number of Years after Radiation Therapy									
		1	2	3	4	5	6	7	8	9	10
1931	1	1	0	0	0	0	0	0	0	0	0
1932	3	3	2	1	1	1	1	1	1	1	1
1933	1	1	1	1	1	0	0	0	0	0	0
1934	5	3	2	1	0	0	0	0	0	0	0
1936	4	1	0	0	0	0	0	0	0	0	0
1937	1	1	1	0	0	0	0	0	0	0	0
1938	4	4	2	2	2	1	1	1	1	1	1
1939	3	1	0	0	0	0	0	0	0	0	0
1940	3	3	2	1	1	1	1	1	1	1	1
1941	1	0	0	0	0	0	0	0	0	0	0
1942	3	2	1	0	0	0	0	0	0	0	0
1943	3	1	1	1	1	1	1	1	1	1	1
1945	1	1	1	0	0	0	0	0	0	0	0
1947	2	1	1	1	1	1	1	1	1		
1948	2	1	0	0	0	0	0	0			
1949	1	0	0	0	0	0	0				
1950	1	1	0	0	0	0					
1951	3	2	2	2	2						
1955	1										
1956	3										
Cases at Risk	46	42	42	42	42	39	38	37	35	33	33
Number Surviving		27	16	10	9	5	5	5	5	4	4
Per Cent Surviving		64	38	24	21	13	13	13	14	12	12

TABLE IV

SURVIVAL IN CASES OF MALIGNANT LESIONS OF TONSIL TREATED BY INTRAORAL CONE PLUS EXTERNAL ROENTGEN THERAPY

Year of Initial Treatment at University of California Hospitals	New Cases	Number of Years after Radiation Therapy									
		1	2	3	4	5	6	7	8	9	10
1933	1	1	1	1	1	0	0	0	0	0	0
1942	1	1	0	0	0	0	0	0	0	0	0
1944	1	0	0	0	0	0	0	0	0	0	0
1946	3	3	3	3	3	3	3	2	2	0	
1947	3	2	2	1	1	1	1	0	0		
1948	2	1	1	1	1	0	0	0			
1951	1	1	1	0	0						
1955	1										
Cases at Risk	13	12	12	12	12	11	11	11	9	6	3
Number Surviving		9	8	6	6	4	4	2	2	0	0
Per Cent Surviving		75	67	50	50	36	36	18	22	0	0

of disease for more than five years, and 3 died after seventy-six, seventy-six and ninety-seven months, respectively, with no evidence of carcinoma present at the time of death. A group of 39 patients was treated with external fields between 49 and 100 sq. cm. in size. Of this group, 2 are living without evidence of disease after more than five years; an additional 2 died with no evidence of metastases or recurrence after intervals of one hundred and one and sixty-five months. Twenty-seven patients were treated with an external field of greater than 100 sq. cm. Of this group, 1 is living without evidence of disease after more than five years, and 1 died without evidence of cancer one hundred and sixty-eight months after treatment. As a rule, patients treated through larger fields had more extensive disease, and no conclusions regarding survival as a function of field size can be drawn.

Dose. Tissue doses of up to 6,000 r (in 2 patients, 7,000 r) were used. These doses were attained at a rate of 800 to 1,200 r (tissue) per week, treating 5 or 6 times a week.

Twenty patients received tissue doses of 4,000 r or less; of these none survived twenty-four months. Sixteen patients were treated with a total tissue dose of 4,000 to 5,000 r. One patient so treated is living without evidence of disease at the end of two hundred and eleven months; 2 died without evidence of cancer at the time of death, having survived sixty-five and one hundred and one months; the remaining 13 died with cancer at times of up to fifty-four months. Of the 36 patients who received tissue doses of 5,000 r or more, 7 are living without evidence of disease, 3 having survived beyond the five year period. Six of the patients receiving more than 5,000 r died without evidence of cancer at the time of death; 4 of these survived more than five years. The other 23 are either living with disease present or are dead from carcinoma with survival periods ranging up to fifty-eight months.

Quality. During the eleven year period between July 1, 1936 and June 30, 1947, most of the external roentgen therapy was done with radiation of 9 mm. Cu half-value layer (1,000 kv. roentgen rays). To evaluate the results of this quality of radiation in comparison to that of other qualities, this group of patients was analyzed separately. In these years, 27 previously untreated patients with malignant lesions of the tonsil were seen. Of these, 22 were treated with 1,000 kv. roentgen therapy; of the remainder, 2 with small lesions were treated with intraoral cone, 2 with 200 kv. radiation, and 1 died during treatment.

Among the 22 treated with 1,000 kv. radiation, 10 were without palpable cervical lymph nodes; 2 of these survived five years without recurrence. Of the remaining 12 patients with palpable cervical lymph nodes, there was one five year disease-free survivor. Thus, the survival rate was approximately the same during the period when the majority of patients were treated by this quality of irradiation as was the over-all rate during the entire period of study.

Secondary Therapy. Of the 10 patients with previous tonsillectomy, 5 have died of their disease and 5 are living. Four of the latter are without known recurrence after one, one and one-half, two and one-half and nine years. Three of the 9 patients with previous radiation therapy (2 had been treated by roentgen rays and 1 by radium) lived five years or longer without known recurrence.

Histologic Type. In only two histologic groups were there as many as 10 patients observed for a minimum of five years. Of 28 patients with squamous cell carcinoma at risk longer than five years, 6 survived at least five years. One of 11 patients with transitional cell carcinoma survived over five years.

SUMMARY

1. Results of the review of 82 cases of malignant lesions of the tonsil treated at the University of California Hospitals since 1931 are presented. Fifty-six of these

patients have been followed five years or longer.

2. Data on age and sex incidence, type and duration of symptoms, histologic diagnoses, and incidence of metastases are given.

3. The over-all five year survival rate for all types of radiation therapy was 20 per cent. The five year survival for those treated by external roentgen therapy only was 13 per cent, while that for those treated by intraoral cone and external roentgen therapy was 36 per cent. The difference in survival between these three groups probably cannot be attributed to the method of therapy, but rather to the extent of the lesion at the time of therapy; only the smallest lesions were selected for intraoral cone therapy, and the most advanced patients received only palliative external roentgen therapy.

4. Palliation was often achieved in patients with incurable tonsillar malignancy.

5. The presence of metastases at the time of the initial visit reduced the five year survival from 33 per cent to 9 per cent.

6. No patient receiving a tumor dose of 4,000 r or less survived twenty-four months; all of the five years survivors received in excess of this dose.

7. The five year survival rate was essentially the same for patients treated with 1,000 kv. roentgen rays as for those treated with radiation of other qualities.

Glenn E. Sheline, M.D.
Department of Radiology
University of California
Medical Center
San Francisco 22, California

The authors wish to express their appreciation to Robert S. Stone, M.D., Chairman of the Department of Radiology, for the use of the material of those patients who were treated by him or under his supervision, as well as for his cooperation in the preparation of this manuscript.

REFERENCES

1. Parshall, D. B., and Stenstrom, K. W. Malignant lesions of the tonsil. *Radiology*, 1953, *60*, 564–572.
2. Walker, J. H., and Schulz, M. D. Carcinoma of the tonsil; a review of treatment and its results in a group of ninety cases. *Radiology*, 1947, *49*, 162–168.

VOL. 80, NO. 5

CARCINOMA OF THE PALATINE TONSIL*

By PAUL W. SCANLON, M.D., *Section of Therapeutic Radiology;* VERNON R. GEE, M.D., *Assistant to the Staff;* JOHN B. ERICH, M.D., *Section of Plastic Surgery;* HENRY L. WILLIAMS, M.D., *Section of Otolaryngology and Rhinology; and* LEWIS B. WOOLNER, M.D., *Section of Surgical Pathology*
Mayo Clinic and Mayo Foundation†
ROCHESTER, MINNESOTA

THE present study of carcinoma of the palatine tonsil, which included patients treated at the Mayo Clinic in the period 1945 through 1949, was undertaken primarily because the impression of one of us (Erich) that carcinoma of the tonsil is best treated by interstitial irradiation supplemented with external roentgen therapy is at variance with the general impression held by most radiologists that this problem is best approached by wide-field coverage with roentgen therapy alone. Then, too, the years 1945 through 1949 were a transition period in which the older concepts of the value of the technique of multiple erythema doses were giving way to more general acceptance of so-called high-dose fractional type of roentgen therapy. Today, judging from the overwhelming acceptance of the latter type of therapy, there seems to be little reasonable doubt as to the superiority of this method; yet our present study would at least imply some intrinsic merit to the older techniques which we cannot ignore. Because of the many consultants involved at our institution, there was no uniform plan of therapy for carcinoma of the tonsil during the years under discussion, yet the very diversity of the treatment plans effected afford us some basis for comparative study. It is felt that the results obtained, an absolute five-year survival or salvage of 43 per cent of 46 patients treated, warrant serious consideration of the methods of treatment employed, or at least attest to the value of treating each patient on an individual basis rather than adhering to a set, standard policy of treatment for all.

MATERIAL

The total of 46 patients treated in the period represented by this study does not include those who were diagnosed as having this disease but who preferred to return home for the extended series of treatment needed, nor does it include patients who had received their primary definitive treatment elsewhere and were no longer treatable by any measure when first seen at the clinic. It does, however, include those patients who had been treated elsewhere primarily but who were given additional therapy at the clinic even if only for palliative purposes.

AGE AND SEX DISTRIBUTION

Thirty-nine of the 46 patients (85 per cent) were males, a sex predominance which is in accord with that of most published series. Dutta-Chaudhuri and Roy[3] summarized the male predominance quoted from several authors, as follows: Dutta-Chaudhuri and Roy,[3] 84.9 per cent; Teloh,[6] 98.6 per cent; Walker and Schulz,[7] 84 per cent; Martin and Sugarbaker,[4] 86 per cent; Mattick, 91.3 per cent; Schall, 88.7 per cent; Burnam, 77.5 per cent; and Desponse, 92 per cent.

As expected, carcinoma of the tonsil proved to be a disease primarily of the fifty to sixty-nine year age group. Thus, 2 patients were less than forty years old, 5 were in the forty to forty-nine year group, 15 in the fifty to fifty-nine year group, 20 in the sixty to sixty-nine year group and 4 in the seventy to seventy-nine year group. It is evident, then, that 33 per cent were in the sixth decade of life and 43 per cent were in the seventh decade.

* Presented at the Fifty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 1–4, 1957.
† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE I

SURVIVAL OF PATIENTS ACCORDING TO TYPE OF LESIONS

Lesion	Total Patients		Patients Surviving Five Years	
	Number	Per Cent	Number	Per Cent of Total
Lympho-epithelioma	7	15	6	86
Transitional cell epithelioma	6	13	2	33
Squamous cell carcinoma	25	54	8	32
Adenocarcinoma	3	—	1	—
Adenoid cystic carcinoma (cylindroma)	1	—	1	—
In situ carcinoma	1	—	1	—
Negative biopsy, clinical diagnosis	2	—	0	—
Negative biopsy of primary lesion, positive biopsy of regional lymph nodes	1	—	1	—
Total	46*		20	

* Includes 6 untraced patients presumed dead of their disease.

PATHOLOGIC CLASSIFICATION

On the basis of the literature there does not appear to be general agreement on the pathologic classification of carcinoma of the palatine tonsil. The classification used in this study is shown in Table I.

Transitional cell carcinoma is distinguished from squamous cell carcinoma by the presence of some degree of keratinization in the latter and its complete absence in the former. Lympho-epitheliomas are nonkeratinizing tumors also, but with certain other identifying features including large cells with fairly abundant cytoplasm, large nucleoli and usually an intimate admixture of lymphocytes. It is surprising that in a series of this size there is no reported instance of lymphosarcoma, particularly since this entity comprised a significant percentage of most reported series (5 per cent[1] to 16 per cent[4]). We have no explanation for this except the possibility that the lymphosarcomas of the tonsil that were encountered were part of a generalized process and as such were not indexed as primary malignant lesions of the tonsil.

From our results it would appear that the pathologic nature of these malignant lesions is not closely related to the survival rate except for lympho-epitheliomas, which seem to have a definitely more favorable course (Table I). Again, this is at marked variance with the opinion of Martin and Sugarbaker[4] who reported that lympho-epitheliomas gave the poorest results of all.

PRESENTING SYMPTOMS

By far the most common presenting symptom encountered was sore throat or some unpleasant sensation noted about the pharyngeal aperture, which occurred in 54 per cent of the patients. Next, in descending order of frequency, were painless tonsillar enlargement in 33 per cent; cervical lymph adenopathy or diffuse swelling in the neck in 28 per cent; dysphagia in 13 per cent; bleeding in 4 per cent; earache in 4 per cent; pain in the upper part of the neck in 4 per cent; hoarseness, headache, vertigo and nausea in 2 per cent each; and no presenting complaints in 2 per cent, a small papillary verrucous lesion of the tonsil being detected on routine examination.

METASTASIS

Clinical estimation of the incidence of regional metastasis is somewhat unreliable since the majority of palpable lymph nodes in the presence of a verified primary lesion are not subjected to biopsy, at least at this institution. Martin and Sugarbaker,[4] however, stated that between the years 1930

and 1938 there were 144 dissections of the neck done at their institution on the basis of palpable regional lymph adenopathy after verification of a primary lesion in the head or neck and that in only 8 per cent did the histologic diagnosis fail to support the impression of metastatic carcinoma. Thus it seems a fair assumption that most palpable lymph nodes represent legitimate metastasis, yet some undoubtedly represent an inflammatory condition.

The possibility that the condition of the regional lymph nodes is inflammatory rather than neoplastic makes any attempt at classification of palatine carcinomas according to stages somewhat unreliable. Nevertheless, we have attempted to make such a classification, three stages being arbitrarily defined. Stage 1 lesions included all those entirely confined to the tonsil regardless of the size of the primary lesion. Others have attempted to divide this group into more than one stage on the basis of the actual size of the primary tumor, but it was felt unwise to attempt to discriminate so finely on various physicians' estimates of tumor size. Stage 2 lesions included those with local extension onto the adjacent parts such as the base of the tongue, hypopharynx, palate, nasopharynx or anterior commissure. Stage 3 lesions included those associated with palpable regional lymph nodes. Of the 46 carcinomas studied, 11 were in Stage 1, 10 were in Stage 2, and 25 were in Stage 3. The five-year survival rate was 73 per cent for the patients with Stage 1 lesions, 40 per cent for those with Stage 2 lesions, and 32 per cent for those with Stage 3 lesions.

Of the 25 patients with palpable regional lymph nodes, 22 had unilateral and 3 had bilateral lesions. In 68 per cent of these patients the involvement was confined to lymph nodes of the immediate draining region of the tonsil, namely the jugulodigastric, the upper deep jugular and the submaxillary lymph nodes. In the remaining 32 per cent lymph nodes of the midcervical level or below were involved. Of the 20 five-year survivors, 60 per cent did not have enlarged regional lymph nodes at any time during the course of their disease while 40 per cent did. There were only 2 patients with systemic metastasis other than involvement of the regional lymph nodes, one of whom had involvement of the posterior cranial-nerve group while the other had pulmonary metastasis. Martin and Sugarbaker[4] also observed that visceral metastasis is rare—in only 3 of 29 necropsy cases of tonsillar carcinoma was there such metastasis (mediastinum, stomach and bones).

We attempted to ascertain whether the pathologic nature of the primary lesion had any relationship to the incidence of regional lymph node dissemination. Lympho-epitheliomas seemed to have less tendency to metastasize than did the tumors of the other pathologic subgroups (Table II). As can be seen from Table 1, 6 out of 7 patients with lympho-epithelioma survived five years, a surprising 86 per cent, while the five-year survival rate for patients of the other subgroups was of the order of 30 to 40 per cent. It is recognized that because of the small number of cases involved in each group, the significance of these differences is open to question.

METHODS AND RESULTS OF TREATMENT

In view of the rather unencouraging results of therapy found in the literature, we were surprised to learn of the unexpectedly high five-year survival rate of 43 per cent in

TABLE II

RELATIONSHIP OF METASTASIS TO REGIONAL LYMPH NODES TO THE PATHOLOGIC NATURE OF THE PRIMARY LESION

Lesion	Patients	Per Cent with Lymph Node Metastasis
Lympho-epithelioma	7	28.5
Transitional cell epithelioma	6	66.7
Squamous cell carcinoma	25	60.0
Adenocarcinoma	3	66.7
Miscellany	5	60.0

TABLE III

SURVIVAL OF PATIENTS ACCORDING TO METHOD OF TREATMENT AND STAGE OF DISEASE

Treatment*	Total Patients				Patients Surviving Five Years			
	No.	Stage of Disease			No.	Stage of Disease		
		1	2	3		1	2	3
Tonsillectomy	3	2		1	2	2		
Tonsillectomy, EDT and FT	1			1	1			1
Tonsillectomy, EDT and IT	1	1			1	1		
Tonsillectomy and EDT	2	1	1		1	1		
Tonsillectomy and IT	1			1	1			1
Electrocoagulation	2	1		1	1	1		
Electrocoagulation and EDT	1	1			1	1		
Electrocoagulation, EDT and IT	2		2		0			
Electrocoagulation and IT	3		2	1	3		2	1
Electrocoagulation, FT and IT	3	1	1	1	2	1		1
EDT	4			4	1			1
IT	3	1	1	1	0			
EDT and IT	5		3	2	3		2	1
FT	13	2	1	10	2			2
FT and IT	2	1	1		1	1		
Total	46				20			

* Abbreviations: EDT, erythema dose technique; FT, high dose fractional roentgen therapy; IT, interstitial therapy.

the present series of 46 cases. Of the major series reviewed, Teloh[6] reported a five-year survival rate of 7.2 per cent, Walker and Schulz[7] a rate of 15 per cent, Martin and Sugarbaker[4] a rate of 18 per cent, Parshall and Stenstrom[5] a rate of 26 per cent and Coutard[2] a rate of 32 per cent. In view of our favorable results, we naturally expected that we could glean from our series some information relative to the most efficient management of carcinoma of the palatine tonsil, and yet a look at the analysis of methods of treatment given in Table III will readily explain our complete inability to choose one definitive mode of therapy as being of superior value.

In Table III fractionated therapy refers to tumor doses of the order of 3,500 r in a period of fifteen to twenty days or up to 5,000 r and more in twenty-five days or more. The erythema dose technique refers to a type of therapy that has been almost completely abandoned at the Mayo Clinic; by this technique erythema doses of 550 to 600 r (air) are delivered with conventional therapy to from two to six fields about the face and neck and directed to the primary tonsillar lesion. In this manner tumor doses of 800 to 1,000 r in two days and up to 1,500 to 1,600 r in five or six days are given. This method with or without ancillary measures was associated with a surprisingly good five-year survival rate.

It appears that because of the many different types of treatment employed in this series and the small number of cases in each category no definite statement can be made regarding a preferential type of therapy. Exceptions can be made, however, for many of the commonly held beliefs regarding the most effective management for carcinoma of the tonsil. With very few exceptions most of the authors who have written on the subject favor high-dose external roentgen therapy as the treatment of choice, with or without supplemental interstitial therapy. Yet in our hands this type of therapy used in 20 patients, 7 of whom survived five or more years (35 per cent), and differing in no major respect from the

therapy commonly advocated, did not prove to be a superior one. Of course, the combination of several different modalities of therapy in any one case makes such generalizations extremely difficult and probably inaccurate. It may be, on the other hand, that the use of multiple types of therapy in many cases, rather than adherence to one standard approach for all, is responsible for the improved five-year survival rates reported herein.

It is generally agreed that surgical treatment alone, with or without dissection of the regional lymph nodes, is of little value. Desponse's classic epithet of "surgery of despair" seems to be well justified in view of the experience of almost all authors with the surgical approach alone. In our series, 19 patients (41 per cent) underwent definitive surgical treatment of the primary lesion, that is, either tonsillectomy or electrocoagulation. Thirteen of these (68 per cent) survived five years or more. Yet in view of the ancillary measures undertaken in all but 3 with limited Stage 1 primary lesions, it seems unfair to ascribe to the surgical measures undertaken any intrinsic merit, particularly in view of the discouraging results reported by others employing the surgical approach alone. Whether the surgical removal of some or, rarely, all of the primary lesion, either by excision or electrocoagulation, may have contributed to the improved five-year results remains a matter of conjecture.

Dissection of regional lymph nodes was attempted to some extent in 8 of the 46 cases of our series. The procedure was limited to dissection of the suprahyoid lymph nodes on one or both sides in 5 of the 8 patients, to radical block dissection in 2 and to local excision of an involved lymph node only in 1. Of the 8 patients, 5 survived five or more years. However, 4 of the 5 patients presented no histologic evidence of metastatic involvement of the lymph nodes when excised tissue was examined. Hence, it seems unfair to say that surgical treatment directed toward regional palpable lymph nodes played an appreciable part in the improvement of the five-year survival rate.

Twenty patients received what today might be considered acceptable high-dose fractional roentgen therapy. Seven of these (35 per cent) survived five or more years. Fifteen had Stage 2 or Stage 3 lesions. Thus it appears that this modality of therapy was employed chiefly for moderately advanced to far-advanced disease unsuitable for more local therapy such as surgical excision or interstitial implantation of radon seeds. We have not, however, been able to confirm the widely held belief that high-dose fractional roentgen therapy alone is superior to all other modalities of therapy.

Nineteen patients received some form of interstitial therapy. Exact dosages could not be calculated because of our inability to ascertain the exact volume of the implantation. It is believed, however, that cancerocidal doses were approximated in most cases, being 4,000 to 6,000 r plus whatever external therapy was added afterward. Ten of the 19 patients (53 per cent) survived five years. Again because of the ancillary measures employed in most instances, it is extremely difficult to assess the real merit of interstitial therapy.

The same may be said for the since abandoned erythema dose technique which was employed in 16 cases, many times for palliative purposes only. We are at a loss to explain the five-year survival of 8 patients (50 per cent) which presumably was due to this technique of therapy. How much of the credit for these survivals is due to secondary measures such as concurrent interstitial therapy or surgical measures remains unknown.

Of 46 patients treated, 20 survived five or more years for an absolute survival rate of 43 per cent. There were 6 untraced patients and these were of course presumed dead of their disease. If these are excluded, the five-year salvage rises to 50 per cent. Of the 20 five-year survivors, 7 subsequently died, again presumably of their disease although necropsy records are lacking. Of the 7, 3 died in the sixth post-treat-

ment year, 1 in the seventh, 2 in the eighth and 1 in the ninth.

Of the 13 survivors alive at the time of this study, 1 is alive more than five years after treatment, 1 more than six years, 4 more than seven years, 1 more than eight years, 4 more than nine years and 2 more than ten years.

Thus it can be easily understood that while we are well satisfied, comparatively speaking, with the eventual outcome of therapy in terms of the five-year survival rate, we are unable to indicate which method of treatment, if any, is superior. Most of the authors who have written on the subject have adhered to a single standard policy of treatment for all and it may be that rigid adherence to a predetermined policy works to a disadvantage in the treatment of a disease such as cancer, the manifestations of which are so protean. We have long held that individualization of every malignant disease is a vital factor in the management of cancer, and we have found nothing in the present study to refute this belief.

Unexplained and at times extreme variability in such nebulous but all important factors as tumor behavior and growth characteristics, host resistance, and radiovulnerability many times negates a systematic and logical approach to the problem and has continued to remain the great enigma of cancer therapy.

SUMMARY AND CONCLUSIONS

Of 46 patients who were treated at the Mayo Clinic in the years 1945 through 1949 for carcinoma of the palatine tonsil, 20 survived five years for an absolute five-year survival rate of 43 per cent. Of the 13 patients alive at the time of this study, 1 had survived more than five years, 1 more than six, 4 more than seven, 1 more than eight, 4 more than nine and 2 more than ten years after therapy.

The sex incidence, the age of the patient at the onset of the disease, the pathologic characteristics of the lesions and the incidence of metastasis were in accord with those of most published series in the literature.

As expected, the five-year survival rate was directly related to the stage of the disease at the time of initial treatment. It was 73 per cent for 11 Stage 1 lesions, 40 per cent for 10 Stage 2 lesions and 32 per cent for 25 Stage 3 lesions.

Only lympho-epithelioma, of the various pathologic entities encountered, seemed to have a definitely more favorable prognosis.

Because of the multiplicity of treatment techniques used, and the frequent employment of more than one modality of treatment for any given patient, it was impossible to select any one treatment policy that could be considered as showing a clear-cut superiority. This would imply either unrecognized merit in the individualization of each treatment problem or the existence of some as yet unrecognized vital factor in the management of cancer.

The Mayo Clinic
Rochester, Minnesota

REFERENCES

1. Authors not listed. Neoplasms of hard palate and tonsil. In Special Head and Neck Issue. *Cancer Bull.*, 1955, *7*, 93–94.
2. Coutard, H. Roentgen therapy of epitheliomas of the tonsillar region, hypopharynx and larynx from 1920 to 1926. Am. J. Roentgenol. & Rad. Therapy, 1932, *28*, 313–331.
3. Dutta-Chaudhuri, R., and Roy, H. Cancer of tonsil (observations on 152 cases). *J. Indian M.A.*, 1954, *23*, 533–537.
4. Martin, H., and Sugarbaker, E. L. Cancer of tonsil. *Am. J. Surg.*, 1941, *n.s. 52*, 155–196.
5. Parshall, D. B., and Stenstrom, K. W. Malignant lesions of tonsil. *Radiology*, 1953, *60*, 564–571.
6. Teloh, H. A. Cancer of tonsil. *A.M.A. Arch. Surg.*, 1952, *65*, 693–701.
7. Walker, J. H., and Schulz, M. D. Carcinoma of tonsil; review of treatment and its results in group of ninety cases. *Radiology*, 1947, *49*, 162–167.

VOL. 80, NO. 5

RADIATION THERAPY OF CARCINOMA OF THE PANCREAS*

REPORT ON 91 CASES

By THEODORE R. MILLER, M.D.,† *and* LILLIAN M. FULLER, M.D.‡
NEW YORK, NEW YORK

CARCINOMA of the pancreas is a disease seldom cured by any form of therapy. In most of the cases of cancer of the pancreas, the disease is recognized and properly diagnosed only in its late stages. The symptomatologic studies indicate that there is a latent period in this condition, and, in addition, a long period from the first symptom to the establishment of the correct diagnosis, averaging about 6.4 months in our series of 209 cases of cancer of the pancreas. The presence of jaundice is observed only in 50 to 60 per cent of cases of cancer of the head of the pancreas and is absent in cancers of the tail of the pancreas. Jaundice is a sign of advanced disease. According to Beeler and Beeler,[1] roentgenologic investigation would give positive results in only 40 to 50 per cent of cancers of the head of the pancreas, while it is frequently impossible to differentiate the roentgen findings of carcinoma arising in the periampullary region.[2,27]

Our present knowledge of glucagon, or the hyperglycemic glycogenolytic factor (H.G.F.) and of the alpha cells has not yet reached the stage that it could be applied to the diagnosis of incipient cancer of the pancreas.[5,17,18] Thus, in most of the cases of cancer of the pancreas, we are confronted with an advanced malignant growth when the patients are first seen.

SURGERY OF CANCER OF THE PANCREAS

Total pancreatectomy is advocated by some investigators. The recent work of Honjo,[15] who performed total pancreatectomy both on dogs and men affected with cancer of the pancreas, indicates that postoperative disturbances are not grave and can be controlled with moderate doses of insulin. Hyperglycemia was properly prevented. In fact, the amount of insulin required after total pancreatectomy is small compared with that required for endogenous diabetes. Our experience with 4 total pancreatectomies performed by us indicates that the dosage of insulin is of the order of 35 to 40 units of regular insulin daily. Honjo found, however, that the endocrine function of the pituitary decreased following pancreatectomy. The development of fatty liver in man seems to occur only in exceptional cases. According to Gourevitch and Whitfield,[9] who reviewed 25 cases of total pancreatectomy with a number of survivals of over two years, the postoperative course was marred in some instances by recurrent attacks of ascending cholangitis. Cholangitis was also noted in patients who have had cholecystogastrostomy as well as cholecystoduodenostomy. The frequency of ascending cholangitis in these side track procedures has led to the abandonment of all except choledochojejunostomy or cholecystojejunostomy en Y or enlooped with a subtending anastomosis.

Pancreatoduodenectomy resulted in a high mortality rate in the past, up to 50 per cent in Japan according to Suzki,[26] but has since been reduced to 15 per cent. This coincides with the reduced mortality in this country.[20] No patient in Suzki's series lived more than one year after the operation. Other investigators, as, for example, Dennis and Varco,[7] Jordan and Shelton,[16] Edwards and Jennings,[8] Muir,[22] Brunschwig,[3] Child and Donovan,[4] etc., report much

* From the Department of Surgery and the Department of Radiation Therapy, Memorial Center, New York, New York. Presented at the Eighth International Congress of Radiology in Mexico City, 1956.
† Department of Surgery, Memorial Center, and Pack Medical Group, New York, New York.
‡ M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Former Kress Fellow at Memorial Center, New York, New York.

more favorable results with survival in some cases up to five years. Yet it appears that the enthusiasm for pancreatoduodenectomy is now being replaced by pessimism after analysis of the end results. Actually, the results of this surgical treatment of the disease have been limited largely, except for a few curative operations, to the palliation of jaundice and duodenal obstruction. Many surgeons now feel that cholecystojejunostomy is as effective as pancreatic resection in relieving jaundice and pain and in increasing longevity. The occasional long term survivor seen in any large clinic lends the only stimulus to further surgical efforts at the present time.

In our series of 209 cases of carcinoma of the pancreas, the most striking thing from a historic point of view was that the patient often had symptoms sufficiently severe to cause him to seek medical attention but so vague that neither clinical nor laboratory methods produced an accurate diagnosis. The classic symptoms of pancreatic cancer are the symptoms of advanced disease. For this reason, the surgical attack on the disease must, of necessity, lead to failure in most instances. Some form of excretory pancreatic duct roentgenography appears to be the only hope of earlier diagnosis, though a high index of suspicion in the male in the fifth and sixth decade having vague upper abdominal distress should lead to earlier laparotomy and, therefore, a better survival rate.

Practically all of the 209 patients who were studied had advanced disease. Some were in terminal stages, living only a few days or weeks after admission. The occasional surgical success will not be discussed here. Almost all of the patients, except those *in extremis*, were explored and a diagnosis established by biopsy of the primary tumor. In some, diagnosis was made by biopsy of distant metastases. Side-track procedures were carried out where advisable, and after a short interval averaging three weeks, radiation therapy was begun in 91 or 43.5 per cent of the total series. One hundred and eighteen received no radiation therapy. Judd, in a report of the results of palliative surgical procedures at the Mayo Clinic, showed an average survival time of 10.2 months from the time of diagnosis. Collar and Winfield, in a similar series, reported a survival time of 7.2 months. Relief of jaundice and pain was reported as good in both series. In our series, the patients not treated by roentgen therapy showed an average survival time of 6.1 months. Some of these patients had been subjected to palliative operations as well as biopsy. The measure of palliation is not merely survival time but includes relief of symptoms and some degree of restoration of health.

RADIATION THERAPY OF CANCER OF THE PANCREAS

Richards[24] was the first to treat cancer of the pancreas with roentgen irradiation. The 2 patients so treated remained alive for ten and twenty months, respectively. De Laroquette[6] used the combined treatment of roentgen rays and diathermy with encouraging result, his patient surviving for eight months with considerable reduction in pain and jaundice. Merritt and Rathbone,[21] Hayer,[13] Handley,[11] and others reported similar figures of survival, while Leven[19] obtained less positive results. Two patients died before the effects of the roentgen irradiation was completed; 2 patients lived two and five months, respectively. Pack and McNeer[23] treated 23 patients with cancer of the pancreas. In 11 cases the tumor dose achieved was not available. However, in the other 12 cases, it has been calculated that a tumor dosage of 2,400–3,600 r was delivered with a 200 kv. roentgen ray unit. The average survival period for this group was 9.37 months for intermittent treatment, and 5.06 months for fractionated applications. Twelve patients receiving teletherapy with a radium pack had a survival time of 12.8 months for fractionated applications. The intermittent application resulted in 2.5 months of survival. One patient was given interstitial radium alone and lived six months. More

recent reports by Harper and Lathrop[12] and others give similar figures for the survival of patients receiving roentgen and isotope therapy.

THE PRESENT STUDY

Ninety-one out of 209 cases of carcinoma of the pancreas were treated with irradiation. Practically all of these patients were admitted with advanced disease. Some were *in extremis*, remaining alive for only a few days or weeks. The cases for irradiation were not selected, except that they had been explored, biopsied, and considered inoperable. Thirty-four patients were treated using 180–250 kv., 12 were treated with a 4 gm. teleradium pack, 20 were treated with the 1,000 kv. apparatus, 20 with the 22.5 million volt betatron apparatus. Four cases were treated with interstitial radon seeds alone and one case treated with iridium 192. Radioactive gold, radioactive phosphorus, and radioactive chromic phosphate were used in some cases to control ascites. A number of the patients could not complete therapy because of the advanced state of their disease. Others tolerated therapy well enough to be able to have a second series when recurrence became evident. Patients with widespread metastatic disease did not tolerate the therapy well, and often it was not completed.

The best results were obtained in patients with disease still fairly well localized to the pancreas and regional lymph nodes. Review of the pathologic material gave no indication of which type of tumor might be more radiosensitive. Three of the patients treated by the radium element pack had unusually long periods of palliation: twenty-eight months, sixteen months, and forty months, only to die of recurrence of their disease. Further treatment produced no results. Of the patients treated with the conventional voltages (180–250 kv.) only 2 showed unusual palliation and longevity. One survived fourteen months from the time of irradiation and another a period of eighteen months. Of the betatron-treated cases, one of 20 had excellent palliation, surviving for one year without evidence of disease, but died suddenly of what appeared to be cerebral metastasis. Palliation was good in 6 patients with survival of from six to eight months, and poor in 13. In 5 of the patients, the treatment was incomplete, and 8 had such advanced disease that death was due to intestinal obstruction, embolism or electrolyte imbalance. The dosages with the betatron ranged from 5,000 to 6,400 r in the tumor in the completed cases.

The cases treated with the 1,000 kv. apparatus appeared to have the best palliation. Three cases survived over two years. The tumor dose in each instance was in the order of 5,000 r. Relief of pain and jaundice, and disappearance of the mass were the rule. Except for these 3 cases, increase in length of life was not marked. However, the general condition of the patients and the relief of pain were remarkable.

Probably the best palliative results of irradiation are achieved when therapy is administered in the immediate postoperative period. There are certain patients who, having developed new symptoms after a period of well being followed by side track operations, are also helped by therapy. The reappearance of jaundice, however, is a very ominous sign in that it frequently indicates ascending cholangitis, liver abscess, and massive involvement of the liver by metastatic cancer. Radiation therapy in this situation produced extremely poor results. In 1 or 2 cases, however, treatment directed at the hilus of the liver relieved the jaundice for a short period again.

In our study covering 91 cases of cancer of the pancreas treated by irradiation, 59 had cholecystojejunostomy or choledochojejunostomy either en Y or en loop with subtending entero-enterostomy. Thirty-two of the 91 had been explored and biopsy alone accomplished.

As control for the group of patients receiving therapy, 118 nontreated cases of cancer of the pancreas were observed. In this series, the survival time averaged 6.1 months. The average survival time for the

irradiated group as a whole was 6.6 months after irradiation was begun. Twenty-nine per cent of the patients had subjective improvement lasting from two weeks up to two years and 9 cases or 10 per cent had excellent palliative results. Diabetes was present in only 13 per cent of the cases studied. It was transient in several cases and was improved or reversed in a number of patients who had good palliation.

Considering the results of radiation therapy in cancer of the pancreas, one must keep in mind that the measure of palliation is not merely survival time, but includes the relief of symptoms and some degree of restoration of health. In our series of cases given radiation, except those in very advanced stages, there was often marked improvement in the general condition of the patients. Jaundice often decreased and pain was relieved.

There are many physicians who are of the opinion that radiation therapy should play no part in the management of otherwise hopeless cases of cancer of the pancreas, even if given only as an attempt at palliation. The usual reason given for this opinion is that radiation therapy to the upper abdomen produces such extreme radiation sickness that any palliative result is overshadowed. This has not been our experience at Memorial Hospital. It is our observation that patients whose general condition is still reasonably good tolerate therapy to the upper abdomen almost as well as to the pelvis, provided they are not incapacitated by vomiting prior to the institution of therapy. We all agree that in pancreatic cancer, as in all other forms of malignant diseases, early diagnosis and the early institution of treatment are of utmost importance. But, once we are confronted with the advanced form of cancer, the relief of pain in palliation should not be underestimated.

DISCUSSION

The chief obstacle to the proper treatment of cancer of the pancreas is our present-day inability to diagnose this disease in its initial stage, during its latent period when no specific clinical or laboratory tests are available During this period, which might last for six months or more, no other symptoms except some discomfort and pain in the upper abdomen are evidenced, and an occasional jaundice of varying degrees of gravity might occur. When examined at this latent period of the disease, patients might occasionally show a tendency to a moderate hyperglycemia and an increase in the blood amylase content. Roentgen examination as a rule gives evidence of the disease only after some alterations in the antral portion of the stomach or in the duodenum are present. It has been shown that widening of the duodenal loop, once considered the most common roentgen finding in this disease, occurs infrequently and usually only after the disease is quite advanced.[1]

Thus, the only alternative in the earlier diagnosis of cancer of the pancreas is laparotomy and biopsy which should be performed when a patient, particularly one who is sixty years of age or over, complains of persistent pain in the upper abdominal region, even if there is no sign of jaundice or roentgenographic evidence of alteration of the upper gastrointestinal tract.

If the disease is localized and there are no lesions in the duodenum or the liver, a total pancreatectomy should be the operation of choice. Postoperative carbohydrate disturbances can be controlled in such instances with small doses of insulin, and fatty liver and ascending cholangitis can be prevented by proper dietary control as well as by choledochojejunostomy en Y.

If the disease is advanced and jaundice is present, cholecystojejunostomy is considered by many surgeons as the best palliative measure to relieve pain and jaundice. Indeed, this appears to offer as much as the more radical palliative pancreatoduodenectomy.

Although many physicians[25] and even some radiotherapists[14] are not very enthusi-

astic about radiation therapy of this disease, our findings seem to indicate its value as a palliative measure in relieving pain and minimizing jaundice. The only contraindication is persistent vomiting where irradiation might aggravate this symptom. Our experience indicates that radiation therapy should be initiated shortly after surgery, preferably two to three weeks afterwards.

The over-all picture of our findings showed that radiation therapy improved the general condition of patients, reduced pain, and decreased jaundice. The best results were obtained with the 1,000 kv. apparatus. Radiation sickness was reduced to a minimum[10] and in several instances the survival time was considerably extended. Roentgen therapy did not increase the average survival time, except in 10 per cent of the cases. Thus, this treatment of cancer of the pancreas should be considered only as a palliative measure, an adjunct to surgery. The best results were achieved when the disease, although inoperable, was limited to the local area. The complications of radiation therapy were negligible in the patient whose general condition was relatively good. Palliation in the form of relief of pain, decrease in size of mass, and improvement in the general condition was noted in many of the cases.

In view of the clinical evidence that pancreatic cancer is often sensitive to irradiation, the following method of treatment is suggested: (1) Exploratory laparotomy and biopsy if the patient is considered inoperable; (2) cholecystojejunostomy and gastroenterostomy in the presence of jaundice and duodenal obstruction; (3) implantation of gold filtered radon seeds or seeds of iridium 192, being careful not to exceed a measured tissue dose as the pancreas often becomes necrotic when overdosed; (4) subsequent external irradiation with supervoltage apparatus or a radioactive source in the 1 mev. or better range. Our present plan calls for the use of the cobalt 60 teletherapy and iridium 192 implantation. Further experience with this modality is now being accumulated by Doctor Ulrich Henschke at Memorial Hospital.

SUMMARY

Ninety-one cases of carcinoma of the pancreas were treated by radiation therapy. All cases had been explored prior to irradiation. The average survival time was only 6.6 months after the initiation of radiation therapy and 12.8 months after the initial symptom. In 10 per cent of the cases, radiation therapy achieved excellent results as far as the survival time and general condition of the patient were concerned.

There was no increase in the survival time in the rest of the cases treated with radiation therapy, although relief of pain and decrease in jaundice were achieved as palliative measures.

The complications of radiation therapy were negligible in most treated patients provided they were in good general condition at the onset.

The best results were obtained with the 1,000 kv. roentgen-ray apparatus.

Diabetes was present in only 13 per cent of the cases and was transient in several of the cases or was reversible in a number of patients who had good palliation following radiation therapy.

Theodore R. Miller, M.D.
Pack Medical Group
139 East 36th Street
New York 16, New York

REFERENCES

1. Beeler, J. W., and Beeler, R. C. Barium study of gastrointestinal tract in determining cause of jaundice. *J.A.M.A.*, 1953, *151*, 268–270.
2. Beeler, J. W., and Kirklin, B. R. Roentgenologic findings accompanying carcinoma of pancreas. Am. J. Roentgenol. & Rad. Therapy, 1952, *67*, 576–584.
3. Brunschwig, A. Pancreatoduodenectomy: Curative operation for malignant neoplasms in pancreatoduodenal region; report of 3 over-5-year survivors. *Ann. Surg.*, 1952, *136*, 610–624.
4. Child, C. G., and Donovan, A. J. Surgical aspects of pancreatic disease. *J. Louisiana M. Soc.*, 1956, *108*, 195–204.
5. DeDuve, C. Glucagon; hyperglycaemic glyco-

genolytic factor of pancreas. *Lancet*, 1953, *2*, 99–104.

6. de Laroquette, M. Tumeur du pancréas et de l'estomac traitée par la radiothérapie et la diathermie. *J. de radiol. et d'électrol.*, 1927, *11*, 204.
7. Dennis, C., and Varco, R. L. Survival for more than five years after pancreatoduodenectomy for cancers of ampulla and pancreatic head. *Surgery*, 1956, *39*, 92–106.
8. Edwards, C. R., and Jennings, E. R. Pancreatoduodenectomy for carcinoma of ampulla of Vater; case report and review. *Bull. School Med. Univ. Maryland*, 1954, *39*, 65–70.
9. Gourevitch, A., and Whitfield, A. G. W. Total pancreatectomy. *Brit. J. Surg.*, 1952, *40*, 104–107.
10. Guttmann, R. J. Effect of 2 million volt roentgen therapy on various malignant lesions of upper abdomen. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 204–212.
11. Handley, W. S. Pancreatic cancer and its treatment by implanted radium. *Ann. Surg.*, 1934, *100*, 215–223.
12. Harper, P. V., and Lathrop, K. A. Isotope therapy for carcinoma of pancreas. *Clin. Congr. ACS*, 1954, Nov., 15–19.
13. Hayer. Die Strahlenbehandlung der Krebse des Magens und der in das Duodenum ausscheidenden grossen Drüsen. *Med. Klin.*, 1936, *32*, 1733–1736.
14. Holmes, G. W., and Schulz, M. D. Therapeutic Radiology. Lea & Fibiger, Philadelphia, 1950, p. 243.
15. Honjo, I. Total pancreatectomy. *J. Internat. Coll. Surgeons*, 1956, *25*, 551–557.
16. Jordan, G. L., Jr., and Shelton, E. L., Jr. Significance of jaundice following pancreatoduodenal resection. *J.A.M.A.*, 1956, *162*, 196–197.
17. Kelly, J. D. Diagnosis of islet-cell tumours of pancreas. *Lancet*, 1956, *1*, 668–670.
18. Korp, W., and Lecompte, P. M. Nature and function of alpha cells of pancreas; their possible role in production of glucagon. *Diabetes*, 1955, *4*, 347–366.
19. Leven, N. L. Experimental study: Effect of radium emanation on pancreas of dogs. *Am. J. Cancer*, 1933, *18*, 899–904.
20. McDermott, W. V., Jr., and Bartlett, M. K. Pancreaticoduodenal cancer. *New England J. Med.*, 1953, *248*, 927–931.
21. Merritt, E. A., and Rathbone, R. R. Diagnosis and roentgen treatment of carcinoma of head of pancreas. *Radiology*, 1936, *26*, 459–464.
22. Muir, E. G. Resection for carcinoma of head of pancreas: Two 5-year survivals. *Brit. J. Surg.*, 1955, *42*, 489–490.
23. Pack, G. T., and McNeer, G. Radiation treatment of pancreatic cancer. Am. J. Roentgenol. & Rad. Therapy, 1938, *40*, 708–714.
24. Richards, G. E. Possibilities of roentgen-ray treatment in cancer of pancreas. Am. J. Roentgenol., 1922, *9*, 150–152.
25. Sanders, L. C., and McBurney, R. Carcinoma of pancreas. *Am. J. Gastroenterol.*, 1956, *25*, 59–65.
26. Suzki, R. Results of pancreatoduodenectomy. Foreign Letters Section. *J.A.M.A.*, 1955, *158*, 501–502.
27. Willy, R. G., and Drymalski, G. W. Carcinoma of tail of pancreas; roentgenographic aspects—2 case reports. *Quart. Bull. Northwestern Univ. M. School.*, 1951, *25*, 276–278.

VOL. 80, NO. 5

ROENTGEN TREATMENT OF GRANULOSA CELL CARCINOMA OF THE OVARY*

By ROBERT BRAY ENGLE, M.D.
PASADENA, CALIFORNIA

GRANULOSA cell tumor is not the rare and seldom the spectacular tumor which most of us recall best from the rather undue emphasis of its hormonal effects as seen before puberty. Actually only about 5 to 10 per cent of these tumors occur before adolescence, so that the sexually precocious female child of our textbook pictures is not a common feature of this neoplasm.

The tumor itself is relatively common, constituting from 1 to 19 per cent of all ovarian tumors observed in various clinics.[7,2] Of 3,800 ovarian tumors seen at the Mayo Clinic, 1.63 per cent were granulosa cell tumors.[10] They contribute 10 per cent of all malignant ovarian tumors.[1,17]

Justification for reporting this group of cases is found in the statement of del Regato:[1] "It is unfortunate that ovarian tumors are so often grouped together in the literature without regard to their pathologic type. This is particularly regrettable in view of the fact that the individual types vary considerably in their response to irradiation." Moreton and Leddy[15] report 11 patients who received radiation therapy and state in their article: "From a review of the literature, it is difficult to draw conclusions regarding the radiosensitiveness of granulosa cell tumors."

AGE INCIDENCE

Five to ten per cent of granulosa cell tumors occur before adolescence, 30 per cent during the child-bearing age, and 60 per cent after the menopause.[4]

PATHOLOGY

Gross Appearance. The size may range from a few millimeters up to large masses filling the abdomen.[17] The largest recorded tumor weighed 35 pounds.[4] The tumors are predominantly solid, occasionally studded with small cysts. They may, however, show marked cystic change as was noted in several in our series. They exhibit a yellow or white color on cut section, but this may be altered by hemorrhage. About 95 per cent are unilateral.[4] The average tumor is said to be lobulated and encapsulated, but more aggressive neoplasms show invasiveness with fixation, local extension or adhesions, peritoneal implants, bilaterality, and occasionally gross metastases. Diddle[3] reports metastases in 110 of 1,189 cases of feminizing mesenchymomas.

Microscopic Appearance. Novak[17] states that in the great majority of cases the morphologic resemblance of the tumor cells to granulosa cells and the evidences of growth characteristics identical with those of granulosal tissue are the most important criteria for diagnosis. These cells are small, polyhedral, slightly basophilic, and have vesicular nuclei. The cells are usually of embryonal type, but may be larger, more adult in appearance, polyhedral, or spindle-shaped.[7]

All authors stress the marked variability of cellular pattern which these tumors present, and the variation within the same tumor (requiring the study of a number of representative sections of each tumor).

It is felt by many that the granulosa cell tumor almost always contains theca cell elements as well. Often these cells are differentiated only by silver stain. The theca cells show argentaffine reticulum surrounding the cells; the granulosa cells show intracellular argentaffine granules but no reticulum.[21]

Classification. A growing custom of recent years is to lump granulosa cell tumors and thecomas in the category of feminizing

* From the Department of Radiology of the Los Angeles County Hospital and the University of Southern California School of Medicine.

mesenchymomas. This classification takes cognizance of the common mesenchymal origin of these tumors and of their common hormonal effects. The clinical behavior of the thecomas shows a number of differences, however. Thecomas only infrequently develop bilaterality, ascites, recurrences, or metastases, and they are rare before puberty. In general, they are much less malignant than the granulosa cell tumors.

Call-Exner bodies are common, representing hydropic degeneration of a tumor cell, usually associated with a satellite rosette of granulosa cells.

The more common cellular patterns noted are the *folliculoid*, *cylindroid* (due to the invasion of connective tissue by the tumor cells, with splitting into columns or cylinders),[17] and *diffuse* or parenchymal. The *sarcomatoid* type may sometimes be indistinguishable from true sarcoma.[7] It will be noted that each of these patterns represents successive tendency towards de-differentiation with greater implied growth potential. Other types described are the gyriform, the pseudoadenomatous,[17] and the cystic type containing large cavities with only a thin layer of granulosal epithelium.[7]

Ewing underlined the confusing array of histopathologic patterns which the tumor may present, and added: "When the structure is atypical, the diagnosis must lean heavily on the character of the endometrium, the enlargement of the uterus, and in children the changes in secondary sex characters, and since these secondary effects may result from some other conditions, the diagnosis of a granulosa cell tumor must sometimes remain in doubt."[7]

The difficulty as regards the classification of these tumors was also emphasized by Busby and Anderson[2] who reviewed 107 feminizing mesenchymomas from the first 500 cases of the Ovarian Tumor Registry. Of a group of 5 expert gynecologic pathologists, there was agreement with the chairman and authors in only 74 per cent of cases. It is of particular interest that a sarcomatous cell pattern was observed in only one of these 107 cases. Kottmeier,[14] however, reports that of 70 cases of granulosa cell tumor at Radiumhemmet 14 were of sarcomatous type. He proceeds to make important distinctions regarding prognosis and treatment based on these cellular differences.

Opinions differ greatly on the nature of granulosa cell tumors. Dockerty[4] believes that 90 per cent are benign, Ackerman[1] that only about 40 per cent are benign, and Norris[16] regards all of them malignant. Novak and Brawner[18] report 9 of 36 cases with recurrence and a malignant course, and Novak[17] refers to the entity as granulosa cell carcinoma in his textbook. No differentiation regarding malignancy is made by some authors. Traut and Marchetti[21] state that 8 of their 54 tumors were clinically and histologically malignant.

CLINICAL COURSE AND PROGNOSIS

The clinical course depends on the invasiveness, rate of growth, and probably the histopathologic appearance of the tumor. It seems likely that the more undifferentiated cellular patterns might not be diagnosed as granulosa cell carcinoma by some observers. Accordingly, relatively malignant cases might tend to be cautiously excluded from some series and more brashly included in others.

Histologic criteria of malignancy may serve as prognostic guide, but the clinical behavior of the tumor must be the final determinant for judging these criteria. Busby and Anderson[2] attempted to grade the tumors after the manner of Broders. Using such grading, patients with histologic Grade 1 lesions showed only 9.5 per cent mortality at five years. There were enough exceptions so that a prediction of the prognosis in any given case remained uncertain.

The mortality rate should give some notion of the malignancy of the tumor. About 25 per cent of traced patients with unilateral disease died.[3] Of the 107 patients reported by Busby and Anderson[2] only 96

were followed five years or more. Of these, 20 per cent were dead, and by seven years, 25 per cent either had died or had recurrent disease. This series includes 17 thecomas which are of a more benign nature. Haines and Jackson[9] report 45 per cent mortality in their traced cases.

Late recurrences are frequent in granulusa cell tumors and a five year evaluation may be misleading. About one-third of the recurrences occur after five years and one-fifth after ten years.[3] Jones and TeLinde[11] report 3 cases with recurrences fourteen or more years following surgery.

The prognosis is more severe when the disease is bilateral (two-thirds die within five years), when ascites is present (40 per cent die), when recurrence develops (45 per cent die), and when the lesion is of large size.[3]

HORMONAL ACTIVITY

The clinical signs and symptoms depend in part on the hormonal activity of the tumor. Elaboration of estrin can be determined by appropriate urinalysis before surgery, and will show marked drop within twenty-four to forty-eight hours after removal of the tumor bulk. Unfortunately, determinations of estrogen function are seldom made, although this should be of diagnostic value in the borderline histologic cases. Features of hyperestrinism vary according to the age of the patient. The amount of estrin production probably varies with the degree of differentiation of the tumor, being most marked in the folliculoid type and minimal in the sarcomatoid type.[21]

Hyperestrinism manifests itself before puberty by precocious sexual development of both primary and secondary sex characteristics. Menstruation occurs, but this is an anovulatory cycle.[17] In the child-bearing age, there may be long episodes of amenorrhea, alternating with heavy flow. After the menopause, there is abnormal bleeding, return of the uterus to normal or premenopausal size, and endometrial hyperplasia. The latter finding on dilatation and curettage may be the only clue to the source of the vaginal bleeding.

Hyperestrinism may result not only in endometrial hyperplasia, but in polyp formation, or adenomyosis. An increased incidence of fibroids, uterine cancer, and breast cancer is also noted in relation with the tumor. Uterine carcinoma developed in 4 per cent of the patients in Kottmeier's series.[14]

TREATMENT

Primary treatment is surgical. If all of the tumor cannot be resected, probably removal of as much as can safely be accomplished will improve later irradiation results. There is evidence that recurrence may develop in the opposite ovary (or elsewhere) even when a pregnancy has intervened. Thus, although many authors believe otherwise, it is advisable that all patients with granulosa cell tumor should have surgical removal of both tubes and ovaries and of the entire uterus. Efforts to save an ovary may result in loss of life.

There is considerable disagreement as regards the radiosensitivity of granulosa cell tumors.[2,3,6,9] Many authors, although describing the surgical procedures in detail, fail to specify the roentgen therapy except to state that it was, or was not given. A number of cases are reported which have shown definite response of residual or recurrent tumor masses to irradiation.[6,9,13,20] In other cases long term survivals were obtained following postoperative radiation therapy.[6,15]

PRESENT SERIES

The present series consists of 12 cases collected from the files of the Radiology Service of the Los Angeles County Hospital. The patients were referred for treatment by the Tumor Board of the hospital. All had a histopathologic diagnosis of granulosa cell carcinoma of the ovary, and apparently only the more extensive and malignant tumors were considered for irradiation. The period under study extended from 1936 to 1957.

Age range was from three to seventy

years. Besides the three year old patient, there were 7 patients ranging from fifteen to forty-four, and 4 patients ranging from fifty-three to seventy years of age.

Gross extent of the lesions at primary surgery was classed after the Kerr and Einstein modification of Heyman's classification of ovarian tumors.[12] Two cases fell into Group I (removal of primary tumor and visible metastases was possible). Both patients later developed recurrences and died. The remainder of the patients fell into Group IIa (partial or total removal of the primary tumor was possible, but there were visible metastases remaining). Two of these were considered early for this broad category, and the remaining 8 as relatively advanced.

Consistency of the tumors was as follows: 5 were cystic (1 of these was a large multilocular cyst filling the abdomen and presenting typical follicular type granulosa cell carcinoma on section), 5 were predominantly solid, 1 was both solid and cystic, and in 1 no description was made.

Four of the 10 tumors were bilateral at initial surgery. This incidence of bilaterality may again reflect the fact that the cases referred for radiation therapy after surgery were relatively advanced.

Size varied, but in 6 cases the tumors were reported as extending above the umbilicus, 2 presented bilateral large pelvic masses, and 4 had single ovarian tumors ranging from 10 to 20 cm. in diameter.

The *malignant character* of the lesions manifested itself by the following findings: (a) 6 patients showed "adhesions" to adjacent structures, usually bowel; (b) 3 had metastases to lymph nodes or omentum; (c) 6 exhibited local extension or invasion, usually of bowel or mesentery; (d) in no case were there peritoneal implants recorded at initial surgery, but they were found in the cul-de-sac at surgery for recurrence in 1 patient, and another developed a mass in the cul-de-sac postoperatively. Ascites was present in 3 patients. The tumor was bilateral in 4 instances.

In 2 patients none of these malignant features were noted, although one of these had bilateral tumors. Both of these patients died of disease, however.

Pathology. Pathologically, these tumors were reported as granulosa cell carcinoma in all cases. Original reports were by Drs. Newton Evans, Hugh Edmondson, Weldon Bullock, or A. L. Brown of the Pathology Department of Los Angeles County Hospital. Complete review of tissues could not be carried out for this report. Such material as was still available for review revealed tumors ranging from the follicular, cylindroid, and sarcomatoid patterns up to several in which the diagnosis—based on histopathologic pattern alone—was borderline. No tissue was available for cutting of new sections, but correlation with other findings seemed to bear out the original diagnosis.

The general impression was gained that correlation of histopathology with survival was not possible in this small series. Two patients, for example, presented follicular type tumors with comparable cellular pattern, and apparently comparable microscopic stigmata of malignancy. One is free of clinical evidence of disease at eighteen years, yet the other died within one year of surgery.

Surgery. Three patients had just one ovary removed. Five had removal of both ovaries and tubes with subtotal removal of the uterus. Two patients had both ovaries and tubes removed and total hysterectomy. In one patient, after removal of the ovaries, the fixed uterus was left behind and a colostomy done because of an invasion of the sigmoid. In one patient only a part of the ovarian tumor could be removed. This last patient is well fifteen years later.

Irradiation was usually begun two to four weeks postoperatively. A dose of 300 r at half-value layer 1 mm. Cu was given daily to one of four 10×15 cm. ports, two anterior and two posterior, until each had a total of 1,800 r (in air). In 4 cases, additional upper abdominal areas were treated.

Results. Four of the 12 patients showed rapid progression of their disease, all dying

TABLE I

Case	Age	Ascites	Bilateral	Cystic	Size	Gross Extent	Surgery	Survival (yr.)	Status
1	31	Large Amount	o	Solid	15×20 cm.	Right ovary, ascites	Total hysterectomy. Bilateral salpingo-oophorectomy	3	Well
2	44	o	o	Solid	20 cm.	Adherent to right pelvic wall, iliac vessels, and right ureter	Total hysterectomy. Bilateral salpingo-oophorectomy	3	Well
3	43	o	Yes	Yes	25×18 cm.	Tumors level of spleen on left and higher on right. Papillary growths on peritoneum. Uterus displaced by adhesions	Subtotal hysterectomy. Bilateral salpingo-oophorectomy	16 7/12	Died September 1954. Cause not known
4	44	o	o	Yes	"Football" level of xiphoid	Loop of ileum attached posteriorly, omentum attached anteriorly, and adhesions to anterior abdominal wall	Subtotal hysterectomy. Bilateral salpingo-oophorectomy	12 4/12	Died Feb. 25, 1952. Carcinoma of gallbladder (autopsy)
5	61	Yes	o	Yes	"About fills abdomen"	Adherent to sigmoid and rectum	Tumor excised (postoperative mass in cul-de-sac)	18 7/12	Well
6 (A)	53	o	o	Yes	Mass 2/3 of way between navel and xiphoid	Attached firmly to sigmoid, ileum, broad ligaments and uterus	Mass aspirated and partially excised		
(B)	56	o	Yes	Solid	5×5×6 cm. Right ovarian tumor	Residual carcinoma, left parametrium. Adenocarcinoma, right ovary. Adenocarcinoma of corpus of uterus	Right salpingo-oophorectomy, total hysterectomy	15	Well

within one year after initial surgery. These patients were three, thirty-six, thirty-eight and seventy years old, respectively.

Another patient (aged fifteen) was subjected to radical surgery in a small hospital in another community just one month after completion of postoperative roentgen therapy. She died of shock three hours after surgery. The result of roentgen therapy in this patient is thus somewhat indeterminate.

One patient was well for two years after surgery, but died eight months later of recurrence.

Of the 12 treated cases, 4 are now alive and well at intervals ranging from three to eighteen and one-half years after surgery. Two other patients lived twelve years and four months and sixteen years and seven months, respectively. One died of unknown cause and the other of carcinoma of the gallbladder (as determined at autopsy). Analysis of these longer survivals is given in Table 1. It will be seen that all represented extensive disease. All patients had large tumors, 5 had adhesions or extension to adjacent organs, 2 had ascites, and 1 patient had a bilateral tumor. The age range of the 4 longest survivors was forty-three to sixty-one years.

SUMMARY

1. Twelve cases of granulosa cell carcinoma of the ovary treated with postoperative irradiation are discussed.

2. Four long-term survivals (twelve to eighteen years) and 2 three year survivals are reported, all in patients with extensive malignant involvement.

3. Some of the survivors had such extensive tumors that the impression is gained that their survival must be attributed to

roentgen therapy. Routine postoperative irradiation is, therefore, recommended.

St. Luke Hospital
Pasadena, California

REFERENCES

1. ACKERMAN, L. V., and DEL REGATO, J. A. Cancer: Diagnosis, Treatment and Prognosis. Second edition. C. V. Mosby Company, St. Louis, 1954.
2. BUSBY, T., and ANDERSON, G. W. Feminizing mesenchymomas of ovary; includes 107 cases of granulosa-, granulosa-theca-cell, and theca-cell tumors. *Am. J. Obst. & Gynec.*, 1954, *68*, 1391–1420.
3. DIDDLE, A. W. Granulosa- and theca-cell ovarian tumors: Prognosis. *Cancer*, 1952, *5*, 215–228.
4. DOCKERTY, M. B. Granulosa-cell neoplasm of ovary. *Proc. Staff Meet., Mayo Clin.*, 1939, *14*, 298–304.
5. DOCKERTY, M. B., and MACCARTY, W. C. Solid ovarian tumors. *Am. J. Path.*, 1940, *16*, 641–645.
6. DUCKETT, H. C., DAVIS, C. D., and FETTER, B. F. Granulosa cell carcinoma of ovary: clinical and pathological review of 17 patients. *Obst. & Gynec.*, 1953, *2*, 611–618.
7. EWING, J. Neoplastic Disease; a Treatise on Tumors. Fourth edition. W. B. Saunders Company, Philadelphia, 1940.
8. FALLS, F. H., RAGINS, A. B., and GOLDENBERG, M. Clinical and pathological studies of feminizing tumors of ovary. *Am. J. Obst. & Gynec.*, 1949, *57*, 1107–1117.
9. HAINES, M., and JACKSON, I. Granulosa-cell tumour of ovary; analysis of 40 cases. *J. Obst. & Gynaec. Brit. Emp.*, 1950, *57*, 737–746.
10. HODGSON, J. E., DOCKERTY, M. B., and MUSSEY, R. D. Granulosa cell tumor of ovary; clinical and pathologic review of sixty-two cases. *Surg., Gynec. & Obst.*, 1945, *81*, 631–642.
11. JONES, G. E. S., and TELINDE, R. W. Curability of granulosa-cell tumors. *Am. J. Obst. & Gynec.*, 1945, *50*, 691–700.
12. KERR, H. D., and EINSTEIN, R. A. J. Results of irradiation of ovarian tumors. AM. J. ROENTGENOL. & RAD. THERAPY, 1945, *53*, 376–384.
13. KOTTMEIER, H. L. Classification and treatment of ovarian tumours. *Acta obst. et gynec. scandinav.*, 1952, *31*, 313–363.
14. KOTTMEIER, H. L. Carcinoma of the Female Genitalia. Williams & Wilkins Company, Baltimore, 1953.
15. MORETON, R. D., and LEDDY, E. T. Granulosa-cell tumor of ovary; with special reference to radiosensitivity. AM. J. ROENTGENOL. & RAD. THERAPY, 1948, *59*, 717–726.
16. NORRIS, E. H. Granulosa-cell carcinoma. *Am. J. Cancer*, 1938, *33*, 538–548.
17. NOVAK, E. Gynecologic and Obstetric Pathology with Clinical Endocrine Relations. Third edition. W. B. Saunders Company, Philadelphia, 1952.
18. NOVAK, E., and BRAWNER, J. N., JR. Granulosa cell tumors of ovary; clinical and pathological study of 36 cases. *Am. J. Obst. & Gynec.*, 1934, *28*, 637–649.
19. SCHULZE, M. Granulosa cell tumor of ovary. *West J. Surg.*, 1939, *47*, 114–125.
20. STOLL, B. A. Radiosensitivity of granulosa cell tumor of ovary. *Med. J. Australia*, 1956, *43*, 1004–1006.
21. TRAUT, H. F., and MARCHETTI, A. A. Consideration of so-called "granulosa" and "theca" cell tumors of ovary. *Surg., Gynec. & Obst.*, 1940, *70*, 632–642.

VOL. 80, NO. 5

LIPOSARCOMA*

CASE REPORTS AND DISCUSSION OF ITS PATHOLOGY, DIAGNOSIS AND TREATMENT

By ALFRED SCHICK, M.D.,† *and* LLOYD S. ROGERS, M.D.‡
SYRACUSE, NEW YORK

LIPOSARCOMA, which occurs in many regions of the body, is most commonly found in the retroperitoneal space, on the shoulders and in the thighs. Regardless of the tumor's location, the radiologist is called upon to assist in the formulation of the diagnosis, and frequently to give his opinion regarding treatment of the patient. There have been reviews of several large series of liposarcoma in the surgical literature,[2,7,11] but there have been only isolated case reports in the roentgenologic literature.[6,8,9] It is the purpose of this paper to discuss the pathology, diagnosis and treatment of liposarcoma with emphasis on the roentgenologic aspects.

REPORT OF CASES

CASE I. Mr. F.A., a sixty-three year old white married male, was first admitted to the Syracuse Veterans Administration Hospital on May 10, 1955, with the chief complaint of a large painful mass on his right shoulder. Three months before admission he first noticed a painless swelling over the right deltoid region. He was unable to remember any trauma or previous mass. There was increase in size of the mass during the following month, after which he sought medical advice. According to the patient, his local physician aspirated about a pint of bloody fluid from the mass, and during the following two months the mass was aspirated about ten times. A week prior to his admission he noted a burning pain in the mass and sought Veterans Administration Hospital care. He had lost about ten pounds in weight in the previous two months. There was no history of abnormal bleeding, ecchymosis or purpura.

On physical examination the patient was a well developed but poorly nourished elderly white male. His temperature was 101.2°F. The only pertinent finding on physical examination was a 5 by 7 inch mass over the right deltoid area extending over the acromial process and into the axilla (Fig. 1). This mass was cystic in character, only mildly tender, and not fixed to bone. The overlying skin was somewhat discolored and showed the sites of several needle punctures. There were several firm, enlarged axillary lymph nodes.

All routine laboratory findings were within normal limits. This included bleeding, clotting and prothrombin times, platelet count and clot retraction. The sanguineous fluid obtained by aspiration was negative on culture, but pathologic examination revealed malignant neoplastic cells. Electrocardiogram and chest roentgenograms were within normal limits. The roentgenogram of the right arm and shoulder revealed a soft tissue mass, but no bone abnormality (Fig. 2).

In the hospital the patient displayed a spiking fever. After the diagnosis of malignancy had been made from the aspirated fluid, an interthoraco-scapular disarticulation was performed on June 16, 1955. He recovered uneventfully, his fever immediately disappeared, and he was discharged on the twentieth postoperative day (Fig. 1). The pathologist's report showed the tumor to be an undifferentiated liposarcoma involving the skin, skeletal muscle, and fascial planes with extensive necrosis and hemorrhage. The axillary lymph nodes were involved with metastatic liposarcoma.

The patient felt well for three months after leaving the hospital. He then began to have mild dyspnea. This progressed, and weight loss, weakness, and anorexia became increasingly severe. He was re-admitted to this hospital five months after discharge. Physical examina-

* From the Radiology and Surgical Services, Veterans Administration Hospital, and the Departments of Radiology and Surgery, State University of New York Upstate Medical Center, Syracuse, New York.
† Chief Radiologist, Veterans Administration Hospital, and Assistant Professor of Radiology, State University of New York Upstate Medical Center.
‡ Chief Surgeon, Veterans Administration Hospital, and Associate Professor of Surgery, State University of New York Upstate Medical Center.

FIG. 1. Case 1. Photographs showing location of liposarcoma and appearance following interthoraco-scapular amputation.

tion and a roengtenogram of the chest suggested massive pulmonary metastatic disease (Fig. 3). There were no signs of local recurrence. The extent of the metastases and the terminal condition of the patient precluded the use of palliative radiation therapy. The patient was treated with sedation as necessary and he expired on his fourth hospital day.

CASE II. Mr. S. S., a thirty-seven year old white mechanic, was admitted to the Syracuse Veterans Administration Hospital on February 15, 1956, with the chief complaint of a painful swollen right foot. His past history revealed that in 1945 while in the Army he dropped a bucket of sand on his right foot. From that time until 1951, he had some pain in the foot and had noticed a small swelling on its dorsal surface. This was not disabling and he continued full activity. In October, 1951, the mass on the dorsum of the foot was excised at a prison

FIG. 2. Case 1. Roentgenogram showing large soft tissue mass surrounding humerus but not involving it.

hospital and a diagnosis of "ganglion" was made without the aid of a pathologist. From that time until his admission, the swelling of the foot had gradually increased until he could not wear a shoe. During the several months prior to his admission, pain also had increased until it was constant and unbearable. The remainder of the past history was noncontributory.

On physical examination the patient was a well developed, alert, rather thin man. The only pertinent finding was an enlarged right foot. This enlargement was caused by two masses about 4 inches in diameter on the dorsal aspect of the foot. The larger of the two masses was on the medial side and projected over the area of the first metatarsal-phalangeal joint. The other mass extended laterally and seemed to be separated from the medial mass on the dorsum of the foot by the extensor tendon to the second toe (Fig. 4). These masses were quite firm, only slightly tender, and were associated with very little increased heat or redness of the overlying skin. The toes and tarsal joints did not appear involved. The pedal pulses were normal, but the veins on the foot and ankle seemed distended. The inguinal lymph nodes were palpable, but were small and soft.

Fig. 3. Case I. Huge liposarcoma metastases in lung and mediastinum (despite their fat content, indistinguishable from metastases from primary tumors other than liposarcoma).

Fig. 4. Case II. Photograph showing liposarcoma of foot.

All routine laboratory findings and the chest roentgenogram were within normal limits. A roentgenogram of the foot revealed a soft tissue tumor displacing the third metatarsal laterally, but there was no evidence of bone destruction (Fig. 5 and 6).

At operation, frozen section was compatible with a soft tissue neoplasm, type undetermined, and a below-knee amputation was performed. The pathology report revealed a differentiated liposarcoma (classification of Stout) of the soft tissue without periosteal or bone involvement.

Since the amputation was above the proximal joint and involved muscle origins, radiation therapy was not deemed necessary.

The patient made an uneventful recovery, learned to walk satisfactorily with a prosthesis, and two years postoperatively was well without sign of recurrent disease.

Case III. Mr. J. T., a thirty-nine year old white married clerk, was admitted to the Syra-

FIG. 5. Case II. Roentgenogram showing large soft tissue mass with changes in metatarsals.

cuse Veterans Administration Hospital for the first time on March 8, 1956, with complaints of anorexia, weight loss, and urinary frequency due to a "recurrent tumor in his abdomen." His past history revealed that in 1943 while in the Army he first noted a slightly painful mass in his right groin. An operation was performed at that time and a right retroperitoneal lipoma was removed. He was well until October, 1947,

FIG. 6. Case II. Changes in the metatarsals consisting of deformity, erosion and slight reactive sclerosis.

when a recurrence of this tumor was diagnosed and was removed. The tumor weighed 410 gm. He recovered uneventfully except for some weakness of the flexor muscles of his right thigh.

In July, 1948, he was again operated upon for recurrence at which time an extensive dissection of the retroperitoneal area was necessary with removal of some of the psoas muscle. The mass removed measured 13 by 13 by 3 cm. and was again diagnosed as a retroperitoneal lipoma.

He was well until October, 1950, when he again noted a mass in his right lower quadrant, alternating diarrhea and constipation, and urinary frequency. Once more he was operated upon and this time two retroperitoneal masses measuring 15 by 4 cm. and 11 by 4 cm. were removed. These were again reported by the pathologist as lipomata with slight acute inflammation.

The patient was asymptomatic until one year prior to his present admission (thirteen years after his original and five years after his most recent operation) when he again felt a mass in his right lower quadrant which continued to grow in size. During the year prior to admission he had increasing anorexia, weight loss of 25 pounds, and urinary frequency.

On physical examination the patient was a well developed, poorly nourished white male. All vital signs were normal. The only abnormal findings on physical examination were in the abdomen and right thigh. The abdomen was very protuberant and there were three old healed surgical scars. In the right lower quadrant there was an indistinct mass which was difficult to outline due to the distention of the abdomen. In the right thigh just below the inguinal ligament there was an orange-sized mass which was thought to be contiguous with the mass in the lower abdomen.

The laboratory findings were within normal limits except for slight anemia and a low prothrombin time which returned to normal with vitamin K therapy.

The chest roentgenogram was normal. Gastrointestinal series, barium enema examination and intravenous pyelography demonstrated a mass with decreased density in the right abdomen and pelvis which displaced the small bowel into the upper left abdomen and also displaced the bladder and right ureter to the left (Fig. 7 and 8). Cystoscopy confirmed the displacement of the bladder anteriorly and to the left.

Fig. 7. Case III. Displacement of ileum superiorly, and elevation and anterior displacement of hepatic flexure and transverse colon by large retroperitoneal liposarcoma. Note areas of increased radiolucency in left lower and right upper quadrants.

A diagnosis of massive recurrent retroperitoneal liposarcoma was made and the patient was prepared for surgery. Ureteral catheters were passed, and at operation a huge fatty tumor was found arising in the right retroperitoneal region and extending into all other quadrants and through the inguinal ring into the thigh. Some psoas muscle and pelvic periosteum on the right where the tumor was adherent had to be removed. Except in these two regions, it was quite well encapsulated (Fig. 9). The total tumor weighed 16 pounds. On pathologic examination this neoplasm proved to be an undifferentiated liposarcoma (Stout).

The postoperative recovery was uneventful. Because of the tumor's size, its malignant nature and adherence to other structures, it was felt that the patient should receive postoperative roentgen therapy. Beginning about three weeks postoperatively he received radiation treatment to the entire abdomen and right inguinal region. A system of four ports was used,

Fig. 8. Case III. Displacement of bladder and right ureter by retroperitoneal liposarcoma. No distinct soft tissue mass can be seen.

and a tumor dose of 3,000 r was given in four weeks. Since then (two and one-half years) the patient has been completely asymptomatic.

PATHOLOGY

There are several classifications of liposarcoma. Ewing[5] introduced a subdivision into the (1) adult cell liposarcoma—a lawless growth of mature fat cells, and (2) embryonal myxoliposarcoma—a tumor which simulates the embryonal growth of fat tissue and which contains myxomatous tissue and fetal fat cells.

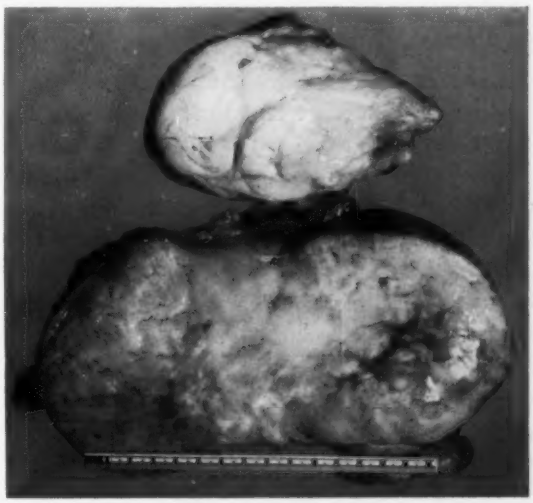

Fig. 9. Case III. Specimen of large retroperitoneal liposarcoma removed surgically.

Stout[11,12] uses a slightly different classification and recognizes: (1) The differentiated liposarcoma. This tumor resembles embryonal fat, and is composed of adult fat cells and lipoblasts. Bizarre cells are absent, and mitotic figures are rare. (2) The poorly differentiated myxoid type of liposarcoma, also called undifferentiated liposarcoma. The characteristic cell of this tumor is a bizarre lipoblast containing misshapen pyknotic or hyperchromatic nuclei. Mitotic figures are frequent. (3) The round cell or adenoid type of liposarcoma. This tumor resembles brown fat in gross appearance. The characteristic tumor cell is spherical with a central nucleus and abundant foamy cytoplasm containing lipoid material.

The differentiated liposarcoma (Stout type No. 1) is a locally infiltrating tumor which seldom metastasizes, but which frequently recurs locally. It is probably this type of tumor which was described as reaching huge dimensions by Delamanter.[4] Other types of liposarcoma are usually more malignant and metastasize frequently, usually via the bloodstream.

The liposarcoma tends to occur in the deeper tissues of the body and the most common sites are the deep tissues of the thigh (40 per cent), the shoulder girdle (8 per cent), and the retroperitoneal space (10 per cent).[7] As can be seen from one of the above cases, the liposarcomata may also occur in areas such as the foot (Case II),[13] and involvement of the hand has also been reported.[7]

The problem of malignant degeneration of a benign lipoma has been discussed by various authors,[7,9,10,11] and it is now the consensus that such degeneration occurs only in very rare instances, usually in patients with multiple lipomata. In the large series reported by Pack and Pierson[7] only 2 cases fulfill their criteria of malignant degeneration of lipoma. One of these was a patient with multiple lipomatosis. Skjoldborg[9] reported a similar case. We believe that the danger of malignant degeneration in a single subcutaneous lipoma is practically nonexistent, but wish to emphasize that the diagnosis of benign lipoma should be accepted with extreme caution if the tumor arises in the deep tissues of the thigh, shoulder, or in the retroperitoneal space. The malignant cells are often in the deepest and least accessible part of the lesion, and in many cases only the pathologically benign portion of the lesion may be obtained for microscopic examination. This can lead to the erroneous conclusion that the entire tumor is benign (Case III).

DIAGNOSIS

Liposarcomata arising in the extremities are usually palpable and their high fat content can be suspected because of their semicystic consistency. Diminished skin temperature overlying the lesion is occasionally a helpful diagnostic sign. Roentgenograms will show the soft tissue mass. In large masses, diminished radiodensity may be apparent. Pressure deformity upon neighboring osseous structures may occur (Fig. 5 and 6), but actual bone invasion has not been reported.

When a liposarcoma arises in the retroperitoneum or mediastinum, roentgenographic examination assumes a position of prime importance since these tumors may be impossible to palpate. In the mediastinum the tumor mass will be outlined by the air-containing tissues of the lung, major bronchi and trachea. The tumors, despite their high fat content, will present as soft tissue masses which are indistinguishable from other mediastinal tumors in all reported cases (Fig. 3). In one case[1] the tumor was so large that it filled the entire hemithorax and a diagnosis of extensive pleural effusion was made.

When liposarcoma is primary in the retroperitoneal space, an accurate roentgenographic diagnosis is often possible. Since such lesions are usually of considerable size before the patient presents himself to the physician, displacement of retroperitoneal structures, especially kid-

ney and ureter, is common. In very large tumors, anterior and lateral displacement of intraperitoneal structures will also occur. Because of the high fat content of these lesions, a distinct soft tissue mass is absent on the plain roentgenograms of the abdomen. Instead of the soft tissue mass, areas of increased radiolucency may be seen (Fig. 7). Therefore, it is the combination of a large retroperitoneal tumor mass as shown by displacement of ureters and kidneys, the absence of a well-defined soft tissue mass, and the presence of areas of increased radiolucency which should alert the radiologist to the presence of a fatty tumor, very likely a liposarcoma.

TREATMENT

At present the treatment of choice of liposarcoma is excision. If a fatty tumor is nonencapsulated, fixed and infiltrating, it must be considered potentially malignant and should be treated with wide excision.

Retroperitoneal and mediastinal fatty tumors should all be considered malignant and excised radically with all possible adjacent and adherent structures.

Fatty tumors of the extremities diagnosed as malignant are best treated by radical excision or amputation. The surgeon's choice of procedure will depend on such factors as size, location, mobility, primary or recurrent status, and degree of malignancy. If excision is elected, it must be truly radical and all adjacent muscle groups should be removed widely accompanied by adjacent fascia. Amputation is ordinarily selected in cases with invasion of muscle groups and fascial planes and in those cases with tumors adherent to other deep structures or bone. The amputation should be performed above the next most proximal joint and the origins of all muscles invaded by the tumor.

The use of radiation therapy in addition to surgery will be influenced by the location of the tumor, its size and its cell type. Radiosensitivity is greatest in the myxoliposarcoma (Ewing) or differentiated liposarcoma (Stout) and least for the adenoid type of liposarcoma. Tumors falling into the first category usually show a good initial response to therapy. They have been controlled and occasionally even cured with radiation therapy alone.[7,9] The adenoid and undifferentiated types of liposarcoma are much less radiosensitive. However, when the tumor is small and a dose of 5,000 to 6,000 roentgens can be delivered, sterilization is possible.[11]

Dramatic instances of long-term palliation of patients with recurrent inoperable and metastatic liposarcoma by radiation therapy have been reported.[1,7]

In the largest series (12 cases) reported treated by irradiation alone,[7] one-half showed a regression of 50 per cent or more in size and 2 were eradicated completely. The same authors report that patients treated with wide local excision and postoperative irradiation have a five-year survival rate of 87.5 per cent.

We feel that radiation therapy should be used in the following types of cases: (1) Cases of inoperable primary or recurrent liposarcoma. Since cure is possible, especially in the differentiated type, treatment should be vigorous and a tumor dose of at least 3,000 r should be attained. (2) Cases of obvious or suspected incomplete excision of all tumor at radical operation. Curative type of therapy should be used. (3) Cases with metastatic disease should be treated for palliation. In differentiated liposarcoma (Stout), the response may be dramatic and well reward the therapist for his care and attention.

SUMMARY

Three illustrative cases of liposarcoma are presented with a discussion of the pathology, diagnosis and treatment of this type of tumor. It is shown that the roentgenographic findings are often sufficiently typical to suggest the diagnosis.

The authors feel that radical surgery is the treatment of choice. Radiation therapy is indicated in inoperable primary or

recurrent liposarcomata, after radical surgery if excision is incomplete, and for palliation in metastatic disease.

Lloyd S. Rogers, M.D.
Veterans Administration Hospital
Syracuse 10, New York

REFERENCES

1. Caputo, N. T., and Spaulding, E. D. Mediastinal liposarcoma. *Harper Hosp. Bull.*, 1953–1954, *11–12*, 122–127.
2. DeWeerd, J. H., and Dockerty, M. B. Lipomatous retroperitoneal tumors. *Am. J. Surg.*, 1952, *84*, 397–407.
3. DeWeerd, J. H. Lipomatous retroperitoneal tumors: Urographic findings. *J. Urol.*, 1954, *71*, 421–426
4. Delamanter, J. Mammoth tumors. *Cleveland Med. Gazette*, 1859, *1*, 31.
5. Ewing, J. Neoplastic Diseases: A Treatise on Tumors. Fourth edition W. B. Saunders Company, Philadelphia, 1940, pp. 197–203.
6. McCormick, N. A. Liposarcoma: Case report. *Radiology*, 1946, *47*, 500–506.
7. Pack, G. T., and Pierson, J. C. Liposarcoma; study of 105 cases. *Surgery*, 1954, *36*, 687–712.
8. Perkins, C. W., and Bowers, R. F. Liposarcoma of mediastinum and lung. Am. J. Roentgenol. & Rad. Therapy, 1939, *42*, 341–344.
9. Skjoldborg, H. Embryonal liposarcoma; report of case. *Acta radiol.*, 1953, *39*, 242–248.
10. Sternberg, S. S. Liposarcoma arising within subcutaneous lipoma. *Cancer*, 1952, *5*, 975–978.
11. Stout, A. P. Liposarcoma—malignant tumor of lipoblasts. *Ann. Surg.*, 1944, *119*, 86–107.
12. Stout, A. P. Tumors of Soft Tissues. Atlas of Tumor Pathology. Sect. II, Fasc. 5. Armed Forces Institute of Pathology, Washington, D.C., 1953.
13. Sugar, S., and Murphy, B. M. Liposarcoma of foot; case report. *J. Michigan M. Soc.*, 1955, *54*, 468–469.

VOL. 80, NO. 5

CARDIAC METASTASIS FROM SQUAMOUS CELL CARCINOMA OF THE SKIN OF THE NOSE

REPORT OF A CASE

By S. GORDON CASTIGLIANO, M.D.,* *and* C. JULES ROMINGER, M.D.†
PHILADELPHIA, PENNSYLVANIA

METASTASIS from pure basal cell carcinoma of the skin never occurs. Occasional reports of such cases found in the literature are in error. Theoretic explanations for these cases of metastasis from the basal cell carcinoma exist, but the subject cannot be dwelt upon here.

The incidence of metastasis from squamous cell carcinoma of the skin varies according to its site of origin. When the skin of the face is involved, metastasis is of infrequent occurrence. Most authors report the incidence of regional lymph node metastasis from facial squamous cell carcinoma to be less than 5 per cent.[2,27] At The American Oncologic Hospital in a period of eighteen years, the incidence approximated 7.5 per cent. The incidence drops to about 4 per cent if the cases in which the primary tumor had received inadequate therapy are excluded. Delayed metastasis occurs. In 2 cases, the metastasis developed three and five years, respectively, after successful treatment of the primary lesion. The average grade of the primary tumors which metastasized was 3.2 (grading from 1 to 4 according to Broders).

The relatively more common site of metastasis from primary facial epidermoid carcinoma is in the regional lymph nodes; distant metastasis is far less frequently encountered. No accurate figures relating to distant metastasis are available, but instances, especially in cases of cancer developing from thermal burn scars of long duration, are reported.[24,27,28,29]

Cardiac metastasis from cancers arising in various organs has been reported with increasing frequency in the last twenty years.[1,3–6,10–12,16,21–23,25,26,31] We have, however, been able to find only 2 cases in the literature of cardiac metastasis originating from carcinoma of the skin of the head and neck.[5,28] It is the purpose of this paper to report the third case of squamous cell carcinoma of the skin of the face which produced cardiac metastasis.

REPORT OF A CASE

J.S. No. C 10540. This fifty-nine year old white male was first seen at The American Oncologic Hospital on January 3, 1950. In March, 1949 the patient first noted an elevated lesion about 1 cm. in diameter presenting on the free edge of the left ala of the nose at the mucocutaneous junction. This resembled a "cold sore." A physician was consulted who prescribed a salve. The lesion allegedly healed in one week.

Three weeks later, soreness of the left side of the nose was again noted. In June, 1949 the lesion, which had increased in size, was incised, but no drainage resulted. During the next two months, the lesion was incised three more times. Not until August 28, 1949 was a biopsy performed. Roentgen therapy was then administered sporadically during the following three months. A total of 8,500 r (in air) was given (factors unknown). The patient's pain increased and the left ala of the nose sloughed.

Because of the gradually advancing neoplastic disease and the necrotic nasal structures, the patient was referred to a plastic surgeon. He, in turn, referred the patient to the Head and Neck Service of The American Oncologic Hospital.

On admission an indurated, ulcerated, and destructive lesion was noted involving the entire left side of the nose. The gross visible lesion measured 2.5 cm. × 3.5 cm. in its greatest dimensions. The left ala was completely de-

* Oncologist and Chief, Head and Neck Service, American Oncologic Hospital, Philadelphia, Pennsylvania.
† Associate in Oncology, American Oncologic Hospital, Philadelphia, Pennsylvania; Associate Radiologist, Misericordia Hospital, Philadelphia, Pennsylvania.

stroyed. The nasal septum was exposed for an area of 2.5 cm. in diameter. There was involvement of the columnella, tip, midline and left bridge of the nose and extension to the left naso-labial fold, but no detectable intranasal extension. Clinically demonstrable metastasis was not present. There was no evidence of active radiation reaction in the area, although chronic changes attributable to irradiation were noted. Multiple biopsies of the lesion were interpreted as epidermoid carcinoma, squamous cell type. It was felt that the previous irradiation had been inadequate both in area treated and time-dose relationship, despite the rather impressive high total dose. For this reason, precision preoperative radiation therapy was instituted, utilizing a specially fashioned lead mask in conjunction with both subtarsal and palatal shields.[6,7]

Between January 1, 1950 and February 18, 1950, a total dose of 12,000 r (in air) was delivered to the lesion through a portal measuring 4.2 cm.×4.0 cm. Deep roentgen therapy, using conventional factors and depth dose diffusion techniques, was employed.* A brisk ulcerative reaction followed and the tumor rapidly regressed. Multiple biopsies at the completion of treatment revealed no evidence of residual tumor. The radiation reaction healed slowly with contracture of the left external naris. In May, 1950 (three months later) a biopsy of a residual unhealed area on the mid bridge of the nose disclosed squamous cell carcinoma. On May 31, 1950, the major part of the nose was electrosurgically resected with the exception of a small portion of the right ala. Histopathologic examination of the excised tissue showed no evidence of residual carcinoma. The patient did not develop further recurrence at the site of the local lesion.

On November 20, 1950, a hard mass, presumably a metastatic lymph node, 1 cm. in diameter was noted in the left pre-auricular area. Roentgen therapy was given. Between November 21, 1950 and December 19, 1950, a total of 6,000 r (in air) was delivered to the left pre-auricular area through a portal measuring 4.0 cm.×4.5 cm., using conventional roentgen therapy. On January 10, 1951, five radon seeds, calibrated at 0.9 mc each and filtered with 0.3 mm. of gold, were inserted in an area 1.5 cm. in diameter. This resulted in a total combined tumor dose of approximately 10,500 r. The lymph node enlargement completely regressed. On February 2, 1951, since no evidence of active malignancy was present, an Indian type flap was elevated on the forehead in preparation for plastic reconstruction of the nose.

On March 1, 1951, a hard lymph node 1.5 cm. in diameter was noted in the left infra-auricular area. Aspiration biopsy of this lymph node was performed and the histopathologic report was metastatic squamous cell carcinoma. Between March 1, 1951 and April 3, 1951, a dose of 7,200 r (in air) was delivered to this lymph node through a portal measuring 5.0 cm.×5.5 cm., using conventional roentgen therapy. On April 12, 1951, six radon seeds, calibrated at 1.0 mc each and filtered with 0.3 mm. gold, were implanted in this lymph node in an area measuring 2 cm. in diameter. This resulted in a tumor dose of 12,250 r. Following this treatment the lymph node enlargement completely disappeared.

After a few weeks, widespread lymph node metastasis developed in the left cervical region. Aspiration biopsy was performed and the histopathologic report was metastatic squamous cell carcinoma. Roentgen therapy was instituted utilizing a combination of 200 kv. peak conventional and 1.75 mev. supervoltage rays. Between June 19, 1951 and August 31, 1951, a total of 14,700 r (in air) was delivered to the left neck resulting in a tumor dose of 11,900 r.

The patient was hospitalized during the course of treatment. Attacks of carotid sinus syndrome developed and persisted during the first six weeks of irradiation. These attacks disappeared as the mass regressed and the pressure was relieved. Despite the immediate benefits from radiation therapy, the patient's condition continued to deteriorate. Multiple metastatic skin lesions appeared, involving the skin between the nasal area and the left neck. These were treated with palliative doses of intermediate voltage roentgen therapy* (Fig. 1 and 2).

In October 1951, metastatic lesions were discovered in the right lung. Uncontrollable bronchopneumonia complicated by multiple pulmonary abscesses shortly supervened. No

* The factors of conventional therapy are: 200 kv. peak; 20 ma.; 40 cm. target skin distance; 1.0 mm. Cu, 1.0 mm. Al filter; half-value layer 1.2 mm. Cu; 300 r—in air—daily.

* The factors were: 140 kv.; 15 ma.; 21 cm. target skin distance; inherent filtration eq. 0.25 mm. Cu; half-value layer, 0.12 mm. Cu.

Fig. 1. Frontal view of patient several months before death. Note absence of external nasal structures with exception of the right ala. The ink marks on the left side of the face encircle multiple areas of cutaneous metastasis.

Fig. 2. Profile view of patient. Note multiple areas of cutaneous metastasis on left side of face and the atrophic skin areas following irradiation of lymph node metastasis in the pre-auricular and submastoid regions.

cardiac symptoms developed prior to death, which came on November 10, 1951.

Postmortem Examination. At autopsy the body was that of a moderately emaciated male. The nose, almost completely absent as a result of surgical and radiation therapy of carcinoma, presented no evidence of neoplastic residue. Involving the skin of the left side of the face were multiple skin nodules measuring from 0.5 cm. to 1.5 cm. in diameter and multiple areas of atrophy secondary to roentgen therapy. No evidence of residual or recurrent carcinoma was found in the treated pre-auricular and infra-auricular areas.

A dense mass 4 cm. × 6 cm. was present at the carotid bifurcation and extended to the mastoid process. An attempt was made to separate this mass from the carotid artery, but it was so firmly adherent to the vessel that *en masse* removal was necessary. The internal jugular vein was thrombotic and heavily invaded by tumor (Fig. 3).

Examination of the chest revealed both lungs to be involved by a bronchopneumonic process.

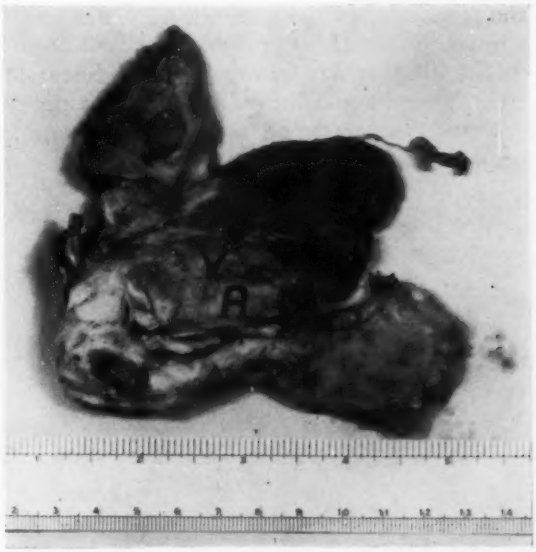

Fig. 3. Metastatic mass removed in *toto* at autopsy. Note intimate adherence to carotid artery (A) and internal jugular vein (V). The latter was grossly invaded by tumor.

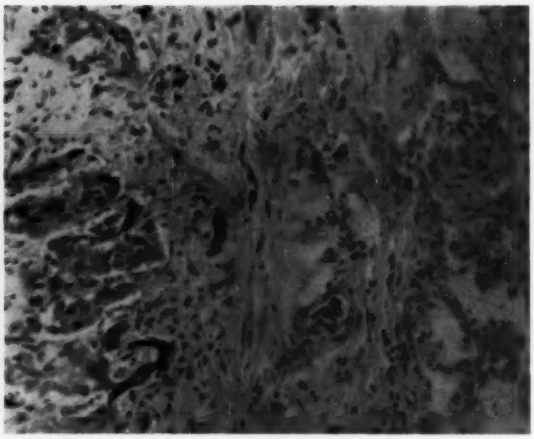

FIG. 4. Photomicrograph of lung showing differentiated metastatic squamous cell carcinoma.

Multiple metastatic lesions were present in both lungs (Fig. 4). Cavitation and abscess formation were present in many of these. The heart was normal in size, but the myocardium on sectioning contained 8 firm white metastatic lesions, 1 cm. to 1.5 cm. in diameter (Fig. 5 and 6).

The kidneys were of normal size, but each contained 5 firm, white metastatic nodules varying from 1 cm. to 1.5 cm. in diameter. The left adrenal gland contained a single 1 cm. metastatic deposit. The right adrenal gland and the remainder of the genitourinary tract were normal.

The liver, spleen, pancreas, gastrointestinal tract, thyroid gland, remaining lymph nodes, osseous structures, and the brain were within normal limits.

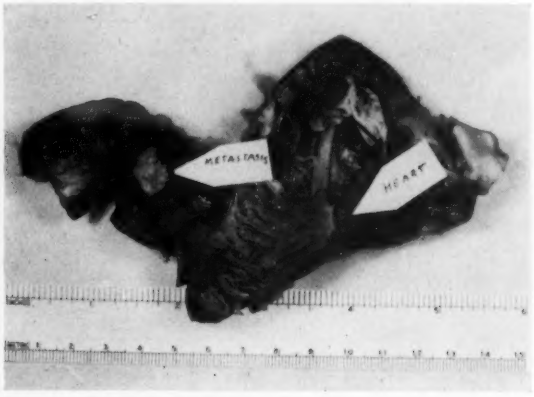

FIG. 5. Gross specimen of heart. Note areas of metastatic squamous cell carcinoma in wall of the right ventricle and interventricular septum.

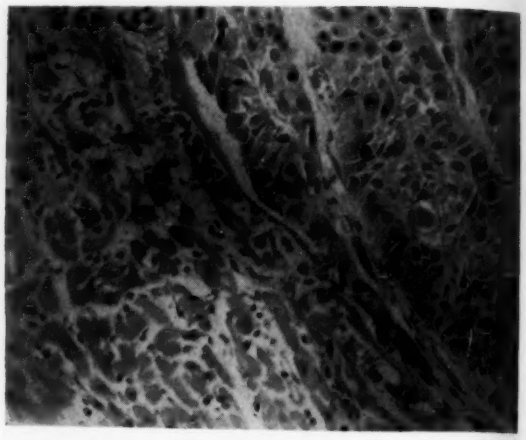

FIG. 6. Photomicrograph of heart. Note areas of squamous cell carcinoma invading the striated cardiac muscle.

Histopathologic examination of all the metastatic lesions revealed epidermoid carcinoma, squamous cell type.

The final diagnoses were: (1) squamous cell carcinoma, skin of nose (controlled); (2) metastatic squamous cell carcinoma, skin of cheek (uncontrolled); (3) metastatic squamous cell carcinoma, left cervical lymph nodes (uncontrolled) with jugular vein invasion; (4) metastatic squamous cell carcinoma, *heart*, lungs, kidneys and left adrenal gland; and (5) bronchopneumonia and pulmonary abscesses.

DISCUSSION

The terminal complications of cancer of the skin of the face usually are hemorrhage, inanition, bronchopneumonia, necrotizing pneumonia, intracranial invasion with meningitis, and inherent toxemia of uncontrolled neoplasm.[8] At the time of death the tumor itself generally is still localized, with a variable degree of contiguous invasion and destruction and at worst exhibits no more than regional extension. However, the local lesion is the initiating cause of death. It sets in motion the events which lead ultimately to the complications culminating in death.

When distant metastasis does rarely occur from squamous cell carcinoma of the skin of the face, the regional lymph nodes are nearly always extensively involved. In contrast to other forms of cancer then, dis-

tant metastasis is rarely the cause of death in facial cancer and never constitutes a clinical problem in the evaluation of the management of the primary lesion. When distant metastasis does complicate squamous cell carcinoma of the skin of the face, the primary lesion nearly always remains uncontrolled over a long period of time. As in oral cancer, distant metastasis occurs when lymph node metastasis invades the jugular vein.[27] After such invasion, dissemination can develop to any organ of the body. This sequence was observed in our case.

Metastatic tumor to the heart may occur from any organ which is the site of metastasizing malignant disease. The diagnosis is seldom made before death. Very extensive involvement may be present without disturbance of cardiac function.

In the present days of earlier diagnosis and more adequate treatment of these lesions, it is expected that lymph node metastasis will be encountered even less commonly and that distant metastasis will practically never occur. This case report serves to emphasize the vital importance of prompt diagnosis and adequate treatment of even the smallest facial cancers which too often are regarded as rather innocuous lesions.

SUMMARY

1. Regional lymph node metastasis from squamous cell carcinoma of the skin occurs in about 5 per cent of the cases.

2. Distant metastasis from squamous cell carcinoma of the skin of the face is rare.

3. The third case of cardiac metastasis from squamous cell carcinoma of the skin of the face is reported.

4. Cases of this type serve to emphasize the vital importance of prompt diagnosis and adequate treatment of even the smallest and most harmless appearing facial cancer.

S. Gordon Castigliano, M.D.
American Oncologic Hospital
Philadelphia 4, Pennsylvania

We acknowledge our gratitude to Dr. A. J. Donnelly and Mr. Philip A. Cerniglia for their efforts in making the photomicrographs.

REFERENCES

1. Abrams, M. L., Spiro, R., and Goldstein, N. Metastases in carcinoma; analysis of 1,000 autopsied cases. *Cancer*, 1950, *3*, 74–85.
2. Ackerman, L. V., and del Regato, J. A. Cancer: Diagnosis, Treatment and Prognosis. Second edition. C. V. Mosby Company, St Louis, 1954.
3. Bisel, H. F., Wroblewski, F., and La Due, J. S. Incidence and clinical manifestations of cardiac metastasis. *J.A.M.A.*, 1953, *153*, 712–715.
4. Burke, E. M. Metastases in squamous cell carcinoma. *Am. J. Cancer*, 1937, *30*, 493–503.
5. Burke, E. M. Metastatic tumors of heart. *Am. J. Cancer*, 1934, *20*, 33.
6. Campagna, M., and Hauser, G. M. Malignant condition of pericardium. *J.A.M.A.*, 1928, *90*, 1362.
7. Castigliano, S. G. In: Cancer of the Skin in Dermatology. S. Greenbaum, Editor. F. A. Davis Company, Philadelphia, 1949.
8. Castigliano, S. G. Master facial cast for rigid portal delimitation in roentgen therapy of cancer about the face. Am. J. Roentgenol. & Rad. Therapy, 1948, *59*, 19–26.
9. Castigliano, S. G., and Rominger, C. J. Distant metastasis from carcinoma of oral cavity. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1954, *71*, 997–1006.
10. Cohen, G. U., Peery, T. M., and Evans, J. M. Neoplastic invasion of heart and pericardium. *Ann. Int. Med.*, 1955, *42*, 1238–1245.
11. Doane, J. C., and Pressman, R. Ante mortem diagnosis of tumors of heart. *Am. J. M. Sc.*, 1942, *203*, 520.
12. Entiknap, J. B. Analysis of 1,000 cases of cancer with special reference to metastasis. *Guy's Hosp. Rep.*, 1952, *101*, 273.
13. Ewing, J. Neoplastic Disease. Fourth edition. W. B. Saunders Company, Philadelphia, 1941, p. 886.
14. Fishberg, A. M. Auricular fibrillation and flutter in metastatic growth of right auricle. *Am. J. Med.*, 1930, *180*, 629.
15. Halberstaedter, L., and Simons, A. Klinische und therapeutische Erfahrungen beim Hautkrebs: Beobachtungen an 556 Kranken aus den Jahren 1920–1930. *Ztschr. f. Krebsforsch.*, 1930, *32*, 146.
16. Helwig, F. C. Tumors of heart. *J. Kansas M. Soc.*, 1935, *36*, 265.
17. Johnson, R. E., and Ackerman, L. U. Epidermoid carcinoma of hand. *Cancer*, 1950, *3*, 657.

18. LEICHTLING, M., REIBSTEIN, M. B., STEIN, M. H., and BASS, H. E. Carcinoma diagnosed by examination of pericardial fluid. *New England J. Med.*, 1952, *247*, 884–885.
19. LISA, J. R., HIRSCH HORN, L., and HART, C. A. Tumors of heart. *Arch. Int. Med.*, 1941, *67*, 91.
20. LYMBURNER, R. M. Tumors of heart—histopathological and clinical study. *Canad.M.A.J.*, 1934, *30*, 268.
21. MCCANDLESS, F. C., and FALOON, W. F. Diagnosis of metastatic tumor by cytological examination of pericardial fluid; report of case using Shorr's stain. *Ann. Int. Med.*, 1948, *29*, 1157–1168.
22. PEARSON, J. E. G. Myocardial metastasis by bronchial carcinoma and other neoplasms. *Brit. J. Tuberc.*, 1948, *42*, 31–38.
23. PIC, A., and BRET, J. Contribution à l'étude du cancer secondaire du coeur. *Rev. de méd.*, 1891, *11*, 1102. Quoted by Yater.[31]
24. PRICE, L. W. Metastasis in squamous cell carcinoma. *Am. J. Cancer*, 1934, *22*, 1–16.
25. PRICHARD, R. W. Tumors of heart; review of subject and report of 150 cases. *Arch. Path.*, 1951, *51*, 98–128.
26. SCOTT, R. M., and GARVIN, C. F. Tumors of heart and pericardium. *Am. Heart J.*, 1939, *17*, 431.
27. STOUT, A. P. Gross pathology of cutaneous cancer. *Arch. Dermat. & Syph.*, 1946, *53*, 597–598.
28. SUTTON, R. L., and SUTTON, R. L., JR. Diseases of the Skin. Tenth edition. C. V. Mosby Company, St. Louis, 1938.
29. WARREN, S., and HOERR, S. O. Study of pathologically verified epidermoid carcinoma of skin. *Surg., Gynec. & Obst.*, 1939, *69*, 726–737.
30. WILLIS, R. A. The Spread of Tumors in the Human Body. C. V. Mosby Company, St. Louis, 1952.
31. YATER, W. M. Tumors of heart. *Arch. Int. Med.*, 1931, *48*, 627.

VOL. 80, NO. 5

METASTATIC MALIGNANT MELANOMA OF THE KIDNEY SIMULATING A PRIMARY NEOPLASM

A CASE REPORT

By COLVIN H. AGNEW, M.D.*
GALVESTON, TEXAS

PRIMARY neoplasms of the kidney account for only 2 or 3 per cent of all malignant tumors in adults. Of these about 80 per cent are adenocarcinomas of the renal parenchyma and 10 per cent originate in the renal pelvis.[1] No statistics are available giving the incidence of metastatic tumors; apparently the kidney is a rare site of gross metastatic implants. The paucity of metastases in certain organs such as the kidney and spleen in the presence of widely disseminated malignant disease is the subject of considerable speculation and investigation. Certainly there is a great need for determining the factors which govern the success or failure of detached tumor cells to survive and multiply in different organs.

The case presented here is an example of possible occurrence of metastatic melanoma in the renal pelvis. In the differential diagnosis of renal lesions by either intravenous or retrograde pyelography, metastases are usually not considered. In the first place, secondary deposits in the kidneys are uncommon and usually located in the cortex. Secondly, if they are established, they represent a terminal complication and are not sufficiently advanced to cause symptoms during the patient's life. Most authors describe only microscopic lesions, with occasional cases of macroscopic nodules being reported. Consequently, this case, in which the lesion was approximately 2.5 cm. in diameter and the cause of the chief complaint of the patient, seems rare enough to justify its reporting.

REPORT OF A CASE

This fifty-seven year old man was admitted on March 7, 1957, complaining of urinary bleeding on three occasions in the past six months with some frequency, but no burning, hesitancy, dribbling, or pain.

Past history. There had been an iridectomy performed in 1944. There was a hospitalization for glaucoma with hemorrhage in the right eye in 1953. Diabetes mellitus was diagnosed in 1927 for which he is presently receiving insulin therapy. He was hospitalized for diabetic gangrene in January, 1956. There was no family history of cancer.

Physical examination. Blood pressure 140/90. Blindness of the right eye. Ophthalmoscopic examination did not reveal any significant information since one could not see beyond the lens. The skin was entirely normal, and except for decreased arterial pulsations peripherally, there was no significant abnormality.

Laboratory findings. Hemoglobin 12.6; white blood cell count 11,600 with a normal differential. Urinalysis revealed no blood, with an occasional pus cell. Specific gravity, 1.020; albumin 1 plus; reducing substance negative; blood urea nitrogen 30.8 mg. per cent; blood sugar 242 mg. per cent; Penn sero-flocculation test positive.

Hospital course. On March 8, 1957 cystoscopy and retrograde pyelography were performed. At cystoscopy, the bladder was normal, but bloody urine came from the left catheter. Five cubic centimeters of hypaque were injected into each catheter. The pyelogram was interpreted as being normal on the right side and showing a renal cell carcinoma on the left side. Since a nephrectomy was contemplated, it was thought necessary to evaluate the function of the right kidney, and excretory pyelography was performed on March 9, 1957. This examination disclosed that there was no destructive lesion in the left upper pole, but rather an obstructive lesion in the renal pelvis. The roentgenographic diagnosis was changed from renal cell carcinoma to renal pelvis tumor with renal calculus not excluded. There was good function of the normal right kidney. On March 13, 1957, a left nephrectomy was performed

* Assistant Professor of Radiology, University of Texas Medical Branch, Galveston, Texas.

FIG. 1. Retrograde pyelogram, after complete filling and withdrawal of catheters. This film clearly shows the extensive growth of the lesion which has blocked the contrast material from the upper half of the kidney. As indicated in the case report, the diagnosis on the basis of the retrograde pyelogram was a renal cell carcinoma.

through a transabdominal approach. The liver was found to be normal. A "small dark green bean shaped structure" was noted in the greater omentum and was interpreted to be an accessory spleen. This was excised. The renal pedicle was ligated before exploration of the renal area was undertaken. The left kidney including the ureter to the bladder was excised. Later, a second operation became necessary to relieve a small bowel obstruction.

Surgical pathology. Examination of the kidney revealed a reddish-black mass of the pelvis about 2.5×3 cm., which grossly had the appearance of a large, friable, partially organized blood clot. The mass was slightly adherent to the underlying pelvic epithelium.

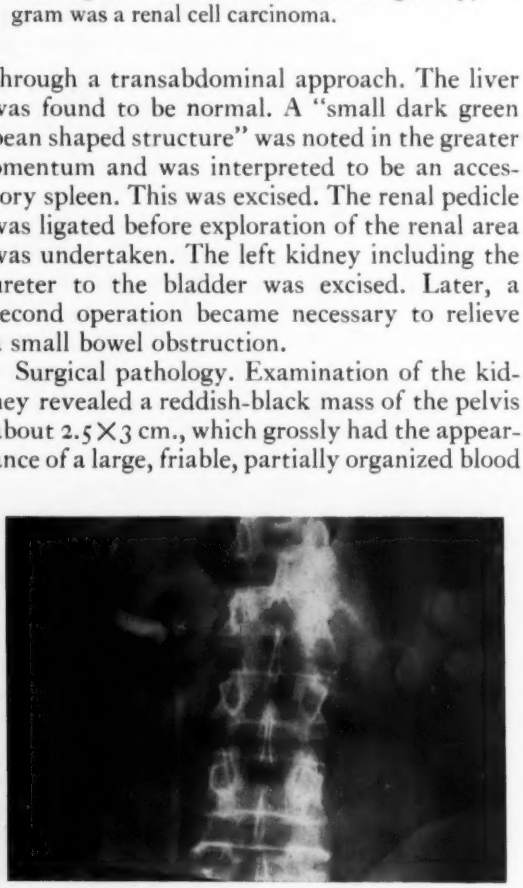

FIG. 2. Excretory pyelogram was made to establish the right kidney function before left nephrectomy. It demonstrates an advanced calyectasis of the upper half of the left kidney with a normal lower pole and a normal right kidney. The diagnosis was changed to renal pelvis tumor.

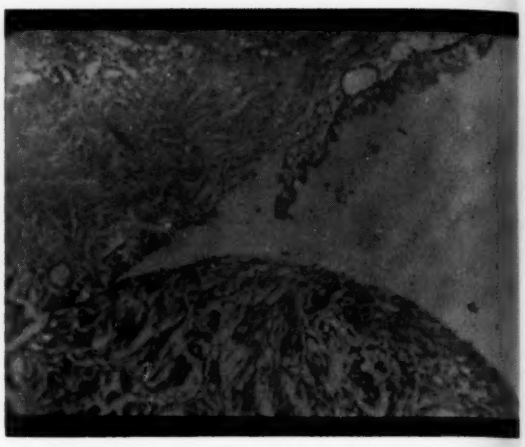

FIG. 3. This microscopic section demonstrates the tumor in its relationship to the renal pelvis. There was no striking invasion of renal tissue.

Microscopic sections of the pelvic tumor exhibited a very cellular neoplasm composed of whorls and fascicles of spindle-shaped, heavily pigmented cells, showing conspicuous nuclear pleomorphism and occasional mitoses with prominent nucleoli and hyperchromatism. Sections of the nodule labelled "accessory spleen" demonstrated metastatic melanoma histologically identical to that described within the renal pelvis.

DISCUSSION

Some speculative suggestions have been made concerning the variability of growth of metastatic lesions. Skeletal muscle, distal bone, heart and the spleen are rarely the site of metastases. On the other hand, the liver and lung are frequently involved. It has been stated that melanocarcinoma is a good example of a tumor which may grow in any organ, and in 50 per cent of the cases deposits may be expected in the heart muscle.[1]

The hypotheses advanced to explain these observations are based: (a) on circulatory mechanics and (b) on the susceptibility of certain organs with metabolic properties to either promote or inhibit the growth of arrested metastatic cells. As regards the first hypothesis, the regularity of metastatic involvement of certain organs,

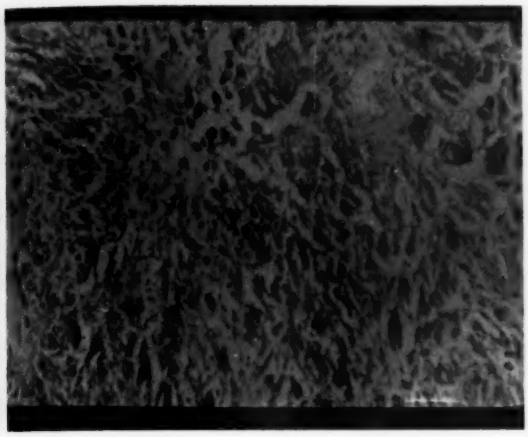

Fig. 4. High powered magnification showing some of the pigment-bearing nuclei.

such as the liver from primary sites of the alimentary tract and the lungs from many organs, supports the contention that the blood volume and vascular pattern enhance the chances of arrest of tumor emboli. On the other hand, if it were simply a matter of blood volume and anatomic structure, then the spleen and kidney should be frequent sites of successful implantation. Furthermore, if it were a simple mechanical phenomenon involving the blood supply and vascular architecture, the chances of lodgment should be greater in the bones of the forearm and leg. These, however, are rare sites; the phalanges are even rarer. These observations make it quite clear that other factors have significant influence upon the survival of metastatic tumor cells.

The second hypothesis postulates that the variations of metastatic growth are related to metabolic properties of the host tissue. Willis[7] gives a comprehensive review of the publications on this subject. One of the most important factors concerns the respiratory needs of the tumor cell. It might be worthwhile to quote Seigo Minami working in Warburg's laboratory with Flexner rat carcinoma on tumor metabolism: "If it (tumor) should be able to utilize this energy liberated by glycolysis, it would be less dependent than normal cells on the supply of oxygen, a circumstance which—it is perhaps permissible to say—would explain the behavior of the tumors in the organism."[5] His assumption about the needs of the tumor cell have been verified; however, it is one thing to measure the respiratory quotient and anaerobic properties of cells after the tumor has made some growth and another to evaluate the circumstances in the organ when the tumor cell becomes arrested.

In the present case the problem was as difficult as might have been expected. The primary lesion was unknown, although it might have been presumed to be in the right eye. In any event, the only two known metastatic lesions had passed through the pulmonary vessels. One successful growth occurred in the omentum. The renal pelvis growth, which had about the same volume as the omental growth must have gone through some small renal vessels to get to the epithelium of the pelvis, or was excreted intact and became implanted in the renal pelvic epithelium.

Rössle[4] published excellent photomicrographs of a breast tumor with metastases in the glomerulus and tubules. He attributed the multiple metastases in the renal pelvis and ureteral mucosa to implantation. This was a case in which all the organs contained metastases. Fagge[2] presented 2 cases of melanuria associated with melanotic melanoma. The first case was that of a fifty-six year old man who at autopsy had

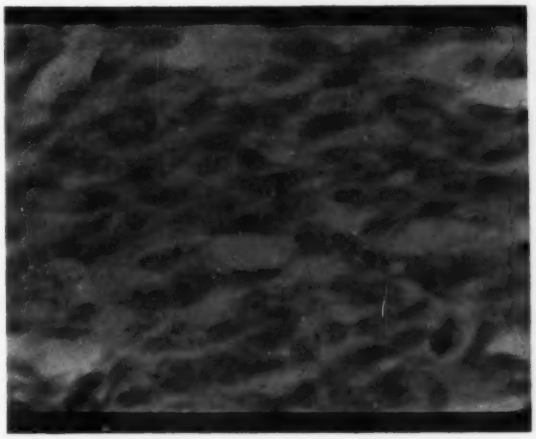

Fig. 5. High powered magnification showing cellular detail with rather conspicuous pleomorphism.

numerous nodules in the lungs and adrenals but no gross renal lesion. Melanuria was found at autopsy. (This was not found before autopsy.) The second case was that of a thirty-three year old man in whom he noted bilateral renal pelvis involvement and a bladder with "black spots, some minute and other millet seed size." The kidney parenchyma was grossly normal, but dark brown. In both of these cases and the breast cancer case of Rössle, the lesions were small and apparently occurring only shortly before death. Oppenheimer[3] expressed the opinion that the neoplastic cell is not excreted as a whole, but only its pigment. He assumed that there was some mechanism in the kidney which prevented the excretion of the intact cell. Willis,[7] in reviewing 31 cases of metastases from tumors of the thymus, found 16 cases with metastases in the kidneys and in several instances the kidneys were the only extrathoracic site of malignant disease. This, coupled with the work of Foulds[7] in which he demonstrated that the intravenous injection of Browne-Pearce rabbit tumor produced growth in 60 of 71 rabbits, primarily in the kidney, adrenal, and eye, supports the contention that the environmental circumstances are more important than the mechanical factors associated with circulation. Turner[5] presented a melanotic sarcoma of the kidney in a young woman who had had an enucleation for "tuberculous trouble" and presented clinically as an acute abdomen. Exploration revealed a retroperitoneal hemorrhage. Almost fourteen months later she had a nephrectomy and at that time a histologic diagnosis of melanotic sarcoma was made. This was the only case I was able to find in which the duration of disease was comparable to our case, but apparently Turner's case was one of a cortical implantation rather than a renal pelvis implantation. Oppenheimer was primarily concerned with the mechanism of pigment excretion, but I believe that our case demonstrates that it is possible for the intact cell to be excreted since it seems unlikely that the metastases occurred by means of a deposit in a terminal arteriole. Had an analysis been made of the urine, it might have demonstrated melanuria as well as hematuria, but it was not specifically looked for.

SUMMARY

The factors which influence the successful implantation and growth of a metastasis are unknown. This is a case report of an infrequent occurrence of metastatic disease simulating primary renal neoplasm. The site of the primary tumor is undetermined but was presumed to be in the diseased right eye.

Department of Radiology
University of Texas
Medical Branch
Galveston, Texas.

REFERENCES

1. Ackerman, L. V., and del Ragato, J. A. Cancer: Diagnosis, Treatment, and Prognosis. Second edition. C. V. Mosby Company, St. Louis, 1954.
2. Fagge, C. H. Two cases of melanuria associated with melanotic new growths. Tr. Path. Soc., London, 1876–1877, *28*, 172–175.
3. Oppenheimer, O. Beiträge zur "Lehre der Pigmentbildung in Melanotischen Geschwülsten." *Virchows Arch.*, 1886, *4*, 515.
4. Rössle, R. Über die Metastasierung bösartiger Geschwülste auf den Schleimhautwege und ihre Bedeutung für das Problem der Malignität. *Arch. path. Anat.*, 1949, *316*, 501–524.
5. Turner, P. Melanotic sarcoma of kidney. *Proc. Roy. Soc. Med.* (*Urology*), *London*, 1920, *14*, 38.
6. Warburg, O., Editor. The Metabolism of Tumours: Investigations from the Kaiser Wilhelm Institute for Biology, Berlin-Dahlem. Translated from the German edition with accounts of Additional Recent Researches by Frank Dickens. Richard R. Smith, Inc., 1931.
7. Willis, R. A. The Spread of Tumours in the Human Body. Second edition. Butterworth & Co., London, 1952.

Vol. 80, No. 5

THE VERTEBRAL PEDICLE SIGN

A ROENTGEN FINDING TO DIFFERENTIATE METASTATIC CARCINOMA FROM MULTIPLE MYELOMA*

By HAROLD G. JACOBSON, M.D.,[1] MAXWELL H. POPPEL, M.D.,[2] JEROME H. SHAPIRO, M.D.,[3] *and* SAMUEL GROSSBERGER, M.D.[4]
NEW YORK, NEW YORK

THE roentgen diagnosis of multiple myeloma, although presenting certain characteristic features, is not always easy. Heiser and Schwartzman[1] described six possible types of skeletal involvement in multiple myeloma. The most common type is that manifested by sharply circumscribed lytic zones, generally associated with osteoporosis. Some cases may show only osteoporosis as a positive roentgen finding. Occasionally, no demonstrable bone involvement is found roentgenographically.

The roentgen findings in metastatic carcinoma usually depend on the primary focus. The major types of bone involvement in metastatic carcinoma are well known. Osteoblastic metastases are most commonly seen with carcinoma of the prostate and carcinoma of the breast. There are numerous sites of primary malignancy which cause osteolytic involvement. Mixed skeletal changes (osteoblastic and osteolytic) are not infrequently encountered in carcinomas of the breast, prostate, thyroid and sometimes in malignant neoplasms of the gastrointestinal tract.

The common sites of skeletal involvement in multiple myeloma and metastatic carcinoma are not significantly different. The spine, skull, pelvis, ribs, femoral and humeral shafts are most frequently involved in both entities. Not infrequently, the radiologist has difficulty in distinguishing metastatic carcinoma from multiple myeloma. This problem may particularly arise in cases of predominantly lytic metastases from carcinoma of the breast. Several differential features have been described as an aid in distinguishing the skeletal lesions of multiple myeloma from the lytic bone lesions of metastatic carcinoma:

1. With spine involvement, a paraspinal mass is encountered more often in multiple myeloma than in metastatic carcinoma.[1]

2. Associated osteoporosis in multiple myeloma is usually quite marked in contrast to the appearance of the uninvolved skeletal structures in metastatic carcinoma. (This finding is probably related to the selective effect on the trabecular and lamellar bone structures caused by the myeloma cells.)[2]

3. The lytic areas seen in the bones of the calvarium in multiple myeloma are generally more sharply circumscribed and more radiolucent than the lytic areas noted in metastatic carcinoma.[2]

In spite of these differential points, difficulty may still be encountered in distinguishing between these two entities roentgenographically.

We have been impressed with the frequency of relatively early pedicle involvement in the lytic type of metastatic carcinoma and conversely with the preservation of the pedicles in multiple myeloma, until very late in the disease.

We have found no specific reference to this differential roentgen sign in any of the literature dealing with metastatic carci-

* From the Division of Diagnostic Radiology, Montefiore Hospital and the Department of Radiology, New York University College of Medicine.
Presented at the Eastern Conference of Radiologists, New York, New York, March 7, 8 and 9, 1957.
[1] Chief, Division of Diagnostic Radiology, Montefiore Hospital, and Clinical Professor of Radiology, New York University College of Medicine.
[2] Professor and Chairman of Radiology, New York University College of Medicine, and Director, Departments of Radiology, Bellevue and University Hospitals.
[3] Associate in Radiology, Montefiore Hospital, and Assistant in Radiology, New York University College of Medicine.
[4] Resident in Radiology, Montefiore Hospital.

TABLE I

METASTATIC CARCINOMA

Primary		Pedicles Involved	Pedicles Intact
Breast	55	53	2
Kidney	6	6	0
Lung	4	4	0
Thyroid	3	3	0
Uterus	2	1	1
Rectum	1	0	1
Pancreas	1	1	0
Ovary	1	1	0
Parotid	1	1	0
Total	74	70	4

noma and multiple myeloma. Pugh[3] states that the spinal column should be carefully examined in the frontal plane with particular reference to the pedicles in searching for metastatic carcinoma. However, no mention is made of the incidence of pedicle involvement in multiple myeloma or the significance of an involved pedicle in differentiating metastatic carcinoma from multiple myeloma. We can find no other reference to this subject.

FIG. 1. Multiple Myeloma. A considerable degree of osteoporosis is present in the lumbar spine. The pedicles are intact.

FIG. 2. Multiple myeloma. Marked osteoporosis and extensive bone destruction is observed in the dorsal and lumbar spine, as well as the ribs and scapulae. The spine pedicles are intact.

CLINICAL MATERIAL

We have evaluated the roentgenograms of the dorsal and/or lumbar spine in 54 cases of proved multiple myeloma. We have also surveyed the roentgenograms of the spine in 74 cases of skeletal (predominantly

TABLE II

MULTIPLE MYELOMA

Pedicles Intact	46
Pedicles Involved	8
Total	54
Incidence of Pedicle Involvement	14.8 per cent

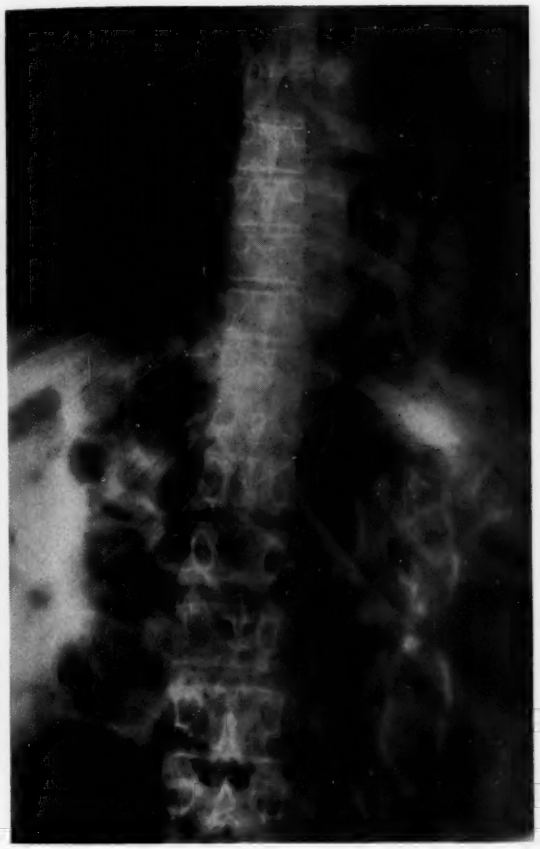

Fig. 3. Metastatic carcinoma from the breast. Partial collapse of the body of D10 with destruction of the left pedicle. Involvement of the right pedicle of L2.

Fig. 4. Metastatic carcinoma from the breast. Osteolytic involvement of the right side of the vertebral body of D11 and the left side of the vertebral body of D12. In both instances the pedicles have been destroyed.

lytic or mixed) carcinoma from various sites (mostly breast) in which one or more spine lesions were present. A summary is given in Table I listing the origin of the primary disease in each instance.

In the 54 myeloma cases, one or two pedicles were involved in 8 instances (14.8 per cent) (Table II). In the 74 cases with carcinomatous metastases involving the spine, one or more pedicles were involved in 70 patients (94.6 per cent) (Table III). The difference between the two groups is statistically significant.* (Table IV).

Table III

METASTATIC CARCINOMA

Pedicles Intact	4
Pedicles Involved	70
Total	74
Incidence of Pedicle Involvement	94.6 per cent

In the 8 cases of pedicle invasion in the myeloma series, five patients showed only one pedicle to be compromised. In 7 of the 8 cases, the amount of pedicular involvement in the roentgenogram was slight. Even with massive skeletal invasion in myeloma the spine pedicles tend to remain relatively intact until very late in the disease (Fig. 1 and 2).

In the 70 cases of partial or complete pedicular destruction in the metastases group, multiple sites of pedicular invasion were frequently seen. The pedicles appear

* The probability of such a difference occurring due to chance alone is 0.0001. The generally accepted level of significance is 0.01.

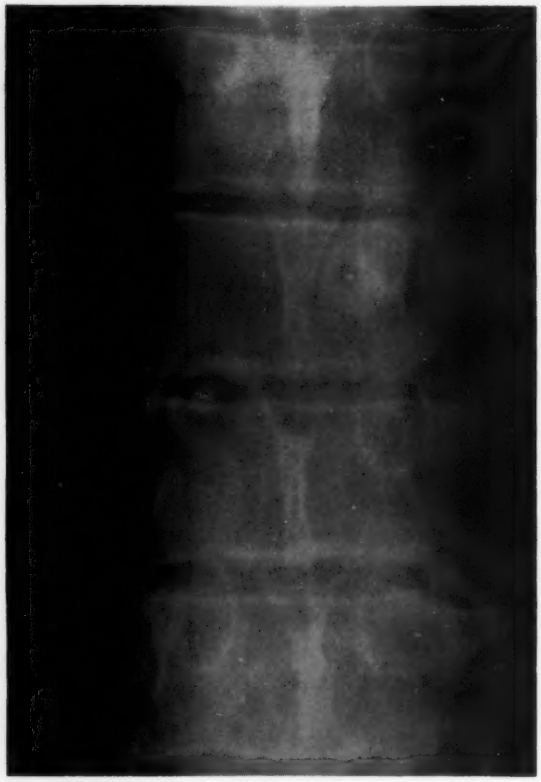

FIG. 5. Metastatic carcinoma from the breast. Obliteration of the right pedicles of D7 and D8. The appearance is that of an eraser having been used to remove each pedicle.

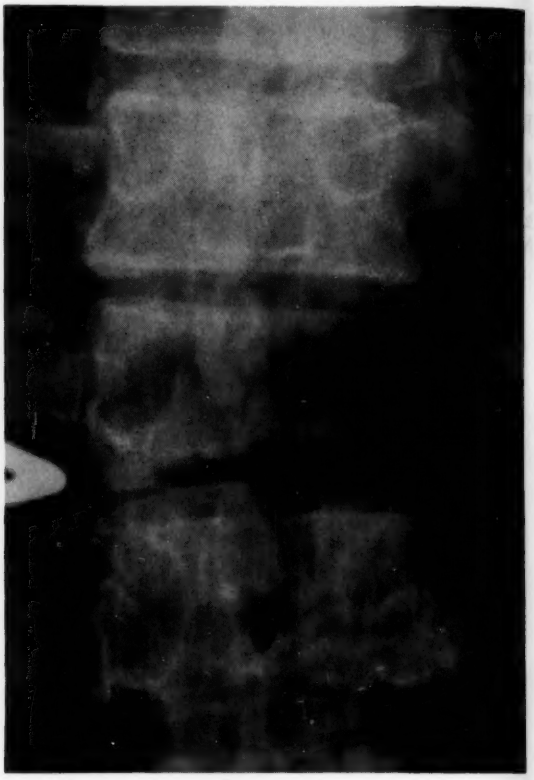

FIG. 6. Metastatic carcinoma from the lung. Destructive lesion in the left half of the body of D11, including the pedicle.

to be almost selectively obliterated early in metastases. We have gained the impression that the pedicle is wiped out as if by an eraser with the surrounding vertebral bone structure appearing relatively intact for quite some time (Fig. 3–6).

DISCUSSION

The pedicle sign has thus proved a useful adjunct in those cases of skeletal involvement where it is difficult to distinguish between multiple myeloma and metastatic carcinomatosis. The reason for the differential pedicular involvement in the two entities may reflect the relative paucity of red marrow in the pedicles as compared with much of the rest of the vertebrae.[4] Multiple myeloma is a disease of the marrow *in situ* with destruction occurring locally and by contiguous extension and pressure. Thus the pedicles in this disease would be relatively spared until very late. Conversely, metastatic carcinoma involving the skeleton (and particularly the spine) is due to embolization of tumor cells. The reason for the early pedicular involvement in carcinomatous embolization remains obscure.

TABLE IV

INCIDENCE OF PEDICLE INVOLVEMENT

Multiple Myeloma	14.8 per cent
Metastatic Cancer	94.6 per cent
Statistical Probability—less than	.0001

SUMMARY AND CONCLUSIONS

A roentgen sign to differentiate multiple myeloma from metastatic carcinoma is presented.

The "pedicle sign" has proved efficacious in a statistically significant series of cases.

A speculative hypothesis explaining the

possible reason for the differential pedicular involvement is given although the reason for early tumor embolization to the spinal pedicles is not known.

Harold G. Jacobson, M.D.
Montefiore Hospital
210th Street and Bainbridge Avenue
New York 67, New York

REFERENCES

1. HEISER, S., and SCHARTZMAN, J. J. Variations in roentgen appearance of skeletal system in myeloma. *Radiology*, 1952, *58*, 178–191.
2. JAFFE, H. L. Personal communication.
3. PUGH, D. G. Roentgenologic Diagnosis of Diseases of Bones. The Williams & Wilkins Company, Baltimore, 1952, p. 87, p. 560.
4. ZIMMERMAN, H. M. Personal communication.

RECENT EXPERIMENTAL CONTRIBUTIONS TO RADIOTHERAPY*

By HENRY S. KAPLAN, M.D.
SAN FRANCISCO, CALIFORNIA

THIS paper presents a brief review of certain aspects of contemporary radiobiologic research, selected for their pertinence to the field of clinical radiotherapy. No attempt has been made to include all phases of radiobiology, nor has any one phase been exhaustively treated. The interested reader is referred to a number of more extensive reviews which have appeared in the past few years.[8,30,73,74]

As often happens, some of the new "discoveries" are really rediscoveries in the laboratory of phenomena noted by astute clinical radiotherapists many years ago. Such rediscoveries are nonetheless of great importance, since the development of new ways to study problems in the laboratory makes possible the kind of systematic and quantitative investigation that can rarely be carried out under clinical conditions. Experimental radiobiology thus deserves the attention of all radiologists as the scientific base on which further progress in radiotherapy largely depends.[50]

It seems convenient to consider the actions of ionizing radiation on tissues under three major headings: (a) effects elicited by radiation events occurring within the cells of interest; (b) tissue responses mediated by radiation effects in the environment; and (c) effects related to the nature and mode of application of the agent.

A. EFFECTS ELICITED WITHIN THE CELL

It has long been known that ionizing radiation reduces the rate of division of mitotically active cells,[24] the duration of the delay being related within limits to the dose received. In addition, radiation may seriously interfere with the integrity of the mitotic process. This may be seen in such phenomena as breakage and crossing-over of chromosomes, non-disjunction (failure of the two halves of a chromosome to pull apart during anaphase, resulting from induced "stickiness" of the chromatin), tripolar and tetrapolar mitoses, and unequal division of chromatin material between daughter cells.[9,51]

Within the past few years much attention has been directed to the question: do these effects result from direct interaction between the radiation and the nuclear material, or are they secondary to effects originally produced in the cytoplasm? Although the observations of Duryee[16] lend some support to the latter proposition, the preponderance of evidence clearly favors a nuclear effect. The elegant experiments of Zirkle and Bloom,[99] and of Uretz, Bloom and Zirkle,[93] with microbeams of protons and of ultraviolet radiation are most convincing in this connection. These investigators found that when such fine microbeams were localized directly over specific regions of individual chromosomes in amphibian heart cells growing actively in tissue culture, very small doses elicited obvious abnormalities in the mitotic behavior of the irradiated chromosome, without affecting the behavior of the remaining chromosomes, which had not been within the field of the beam. In contrast, when the cytoplasm alone was exposed to doses perhaps a thousand fold higher, essentially no subsequent response was noted.

This is not to say that cytoplasmic effects may be disregarded, or even that the cytoplasm is intrinsically less radiosensitive than the nucleus. Mazia[63] has interpreted the differential response of nucleus versus cytoplasm in terms of the number of units

* From the Department of Radiology, Stanford University School of Medicine, San Francisco, California. Presented under the title "Newer Concepts of Tissue Radiation Response" at the Fifty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 1–4, 1957.

associated with any given cellular function. "If my present picture of the nucleus is correct, there is a large number of species of functional units—genes—but very few of each kind. . . . Therefore every bit of damage that is done is likely to show up, because it cannot be covered up by other undamaged units of the same kind. In the cytoplasm on the other hand we know that such important units as enzymes are present in relatively large numbers of each kind. Thus if the nucleus contained two of each kind of gene, ten radiation events might completely inactivate five kinds of genes or produce 50 per cent inactivation of up to ten kinds, while the same number of events would have a completely negligible effect on the cytoplasm, where there are surely thousands or more of each kind of enzyme."

This interpretation may also be the key to understanding the paradox that unusually small amounts of absorbed ionization energy are required to elicit such drastic biologic responses as the killing of a cell, of a tumor, or even of an entire animal.[31] The uniqueness of certain macromolecules in the nucleus creates a vulnerable situation in which an event which is quantitatively insignificant in radiochemical terms becomes of great importance from the standpoint of radiobiology.

The recent work of Puck and Marcus[79] has made it possible to assess the effect of various doses of radiation on the capacity of mammalian cells growing in tissue culture to give rise to future generations of daughter cells. Cells are irradiated within a few hours after having been plated, in much the same manner as bacteria, and are then observed for their capacity to give rise to individual colonies. Using this technique with the HeLa cell (originally derived from a human epidermoid carcinoma of the cervix), Puck and Marcus noted that a dose as low as 96 r could reduce the population to 37 per cent of its normal value. The inactivated cells were observed in some instances to form abortive microcolonies, which were unable to continue division for any prolonged period; more severely injured cells failed to divide at all but continued to increase in mass, becoming giant cells. This phenomenon is not new to radiotherapists, since it has long been known that giant cells may be seen in serial biopsies of irradiated tumors. Indeed, the observation of such cells was one of the considerations that led Failla[20] to the water imbibition theory of radiation-induced cell death. In light of present-day concepts, such cells do not enlarge solely or primarily by imbibition of water; the increase in size results from the fact that the mechanisms which enable the cell to continue building protein and other cytoplasmic components are left largely intact, while those providing for nuclear division have been selectively blocked. Direct support for this view may also be found in the work of Klein and Forssberg[53] with ascites tumor cells.

Glucksmann[27,28] has described another morphologic sequence leading to senescence and death of irradiated tumor cells; namely, an acceleration of normal cellular differentiation to the point where the cell becomes postmitotic and will go on to die, sooner or later, without reproducing itself. It is not yet established whether this is a general effect or one which pertains only to certain types of epithelium.

What is known of the biochemical aspects of cellular radiation injury? Two classes of nucleic acids, desoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are known to occur in all animal cells. Within recent years the respective roles of these two classes of macromolecules have begun to emerge. It now appears that DNA, which is found exclusively in the chromatin of the nucleus, is primarily concerned with genetic functions. For example, purified DNA from one bacterial culture may confer a sustained genetic transformation upon a related but dissimilar culture.[3,46,94] This type of evidence, coupled with increasing knowledge of the enormous structural complexity of DNA, makes it plausible that this is the material of which the genes largely consist, and which is re-

sponsible for their biologic specificity.[87]

RNA is found both in the nucleus, where it is concentrated in the nucleolus, and in the cytoplasm. In contrast to the metabolic inertia of DNA,[86] which increases in amount only preceding mitosis, RNA metabolism appears to bear an essential relationship to the cell's capacity to synthesize new protein. It has been postulated that RNA may exist in a spectrum of specific molecular configurations, each of which may serve as a "template" upon which specific proteins (enzymes, antibodies, hormones) are formed.

With the advent of radioactive isotopes as tracers, it was soon found that the incorporation of various labeled precursors into DNA was specifically inhibited by irradiation at a time which seemed to correlate closely with the time of inhibition of mitosis.[38,43,71,77] It has been tempting to believe that the cell's ability to manufacture new DNA had been selectively injured, and that this biochemical block had to be repaired before the cell could go through mitosis. However, the recent work of Kelly *et al.*,[52] Howard and Pelc,[47,76] and Holmes and Mee[44] indicates that complete mitotic inhibition may be observed at a time when there is no measurable inhibition of isotope incorporation into DNA, suggesting that the mechanisms responsible for the two effects may not be the same. The interesting possibility that part of the inhibitory effect of radiation on DNA labeling may be indirectly mediated is now suggested by Harrington and Lavik.[37] Now that the complexity of this field of biochemistry has become more widely appreciated, it is to be hoped that the effect of irradiation on nucleic acid metabolism will be rapidly clarified, without the pitfalls of misinterpretation which have hampered earlier efforts.

With respect to RNA, the situation is quite different. There is usually no inhibition of isotope incorporation into the RNA of irradiated cells,[40] and the rate at which precursors are incorporated into proteins seems similarly unaffected.[45]

The work of Dale,[13] Barron,[7] Forssberg,[23] and others on the irradiation of purified enzymes in dilute solutions suggested that certain enzymes, particularly those bearing active sulfhydryl groups, were extremely sensitive to rather small doses of radiation, well within the range of usual biologic interest. There is however little evidence that enzymes as they occur within the cell are similarly radiosensitive.[78] The mammalian cell is of course not a simple dilute solution or suspension, but an extremely complex colloidal system within which certain classes of enzymes seem to be confined within sub-structures such as the mitochondria, rather than uniformly dispersed. Moreover, great caution must be exercised in interpreting apparent changes in enzyme activity of irradiated tissues.[21] For example, the observation by several groups[2,15,18,81] that the activity of certain enzymes of highly radiosensitive tissues such as spleen increases strikingly several days after irradiation is more conservatively interpreted as reflecting a change in cell population, due to selective destruction of the more radiosensitive cellular elements, rather than a reflection of a real change in enzyme activity.

In closing this section, we may ask: what has modern radiobiologic research contributed to our understanding of the reasons for the differential radiosensitivity of different classes of cells and tumors? For normal tissues, we now understand that such differences may in part be unreal; that is to say, tissues which seem radioresistant may really have suffered essentially the same injury as the more radiosensitive tissues but they have such an extremely low rate of cell division, and their individual cells have such a long life span, that the morphologic manifestation of the injury is almost indefinitely deferred, thus seeming not to have occurred at all. In contrast, the rapidly dividing tissues must reveal their injury very quickly. This is simply another way of looking at that portion of the old "law" of Bergonié and Tribondeau which holds that radiosensitivity is directly correlated with mitotic rate.

Another part of the "law," which states that radiosensitivity is inversely related to the degree of maturation or differentiation of the cell, has long been known to abound in paradoxes and exceptions, such as the fact that the mature small lymphocyte is far more radiosensitive than its immature stem cell precursors. Another such exception has now been pointed out by Hicks *et al.*[39] who found that the differentiating, presumably postmitotic neuroblast of the embryonic brain is more radiosensitive than the intensely mitotically active primitive cell layer from which it originates.

Differences in mitotic rate and in degree of differentiation certainly do not provide an adequate explanation for the tremendous differences in radiosensitivity exhibited by different types of tumors. Even though it is generally true that the more rapidly dividing and more undifferentiated tumors tend to be more radiosensitive, it is nonetheless also true that two different tumors, both growing at essentially the same rate and having roughly the same degree of differentiation, may be poles apart in their response to radiation.[26] Rapidly growing, anaplastic malignant melanomas or thyroid carcinomas tend to be highly radioresistant, whereas undifferentiated epidermoid carcinomas are usually quite radiosensitive. Numerous other examples readily come to mind. No satisfactory clinical or laboratory explanation for this aspect of differential radiosensitivity has yet emerged. Here perhaps lies one of the greatest challenges to the radiobiologist.

B. EFFECTS ON THE ENVIRONMENT

The importance of radiation effects on the tumor bed has been clearly stated by Shields Warren:[95] "After the usual dose of radiation there is partial or complete recovery of some of the tumor cells and, were it not for the concomitant effects produced on the connective tissue stroma and blood vessels, no lasting effect on an irradiated part would be noted."

Merwin, Algire, and Kaplan[65] made direct microscopic observations of the radiation response of tumor blood vessels in transparent chambers in mice. Initial tumor regression resulting from doses of 2,000 to 5,000 r was followed by recurrent growth from one or more viable foci. However, the irradiated vascular endothelium had become incapable of budding new capillaries to keep pace with the growth of the recurrent tumor nodules, which rapidly outstripped their blood supply and underwent late necrosis on the basis of pressure ischemia. When the bed was pre-irradiated, it failed to provide the usual prompt vascular response for the subsequently introduced tumor. These observations, indicating that radiation injury sustained by the capillary endothelial buds plays an important role in tumor therapy, have been extended recently by Merwin and Hill.[66]

Clinical radiotherapists have long been aware of the tendency for tumors in a densely scarred or otherwise ischemic region to be more radioresistant than the same histologic variety of neoplasm would otherwise be. Recurrences of tumors often spring from the margins of necrotic zones. Moreover, Schwarz in 1909 noted that ischemia induced by pressure on the skin could reduce the intensity of the cutaneous erythema reaction.

All of these clinical observations point to the oxygen content of the blood, and that within the tumor cells themselves, as an important factor in radiosensitivity. This phenomenon has now been rediscovered in experimental radiobiology. Many species of microorganisms, plants, and several solid tumors of mice have been shown to exhibit a distinct oxygen dependence in their response to radiations of low specific ionization. However, it was not until recent years that Gray and his associates[32,33] clearly expounded the potential therapeutic implications of the oxygen effect. They reasoned that since many tumors tend to outgrow their blood supply, nests of anoxic, relatively radioresistant cells might persist and ultimately lead to tumor recurrence. Added support for this concept came from the careful histopathologic studies of irradi-

sponsible for their biologic specificity.[87]

RNA is found both in the nucleus, where it is concentrated in the nucleolus, and in the cytoplasm. In contrast to the metabolic inertia of DNA,[86] which increases in amount only preceding mitosis, RNA metabolism appears to bear an essential relationship to the cell's capacity to synthesize new protein. It has been postulated that RNA may exist in a spectrum of specific molecular configurations, each of which may serve as a "template" upon which specific proteins (enzymes, antibodies, hormones) are formed.

With the advent of radioactive isotopes as tracers, it was soon found that the incorporation of various labeled precursors into DNA was specifically inhibited by irradiation at a time which seemed to correlate closely with the time of inhibition of mitosis.[38,43,71,77] It has been tempting to believe that the cell's ability to manufacture new DNA had been selectively injured, and that this biochemical block had to be repaired before the cell could go through mitosis. However, the recent work of Kelly *et al.*,[52] Howard and Pelc,[47,76] and Holmes and Mee[44] indicates that complete mitotic inhibition may be observed at a time when there is no measurable inhibition of isotope incorporation into DNA, suggesting that the mechanisms responsible for the two effects may not be the same. The interesting possibility that part of the inhibitory effect of radiation on DNA labeling may be indirectly mediated is now suggested by Harrington and Lavik.[37] Now that the complexity of this field of biochemistry has become more widely appreciated, it is to be hoped that the effect of irradiation on nucleic acid metabolism will be rapidly clarified, without the pitfalls of misinterpretation which have hampered earlier efforts.

With respect to RNA, the situation is quite different. There is usually no inhibition of isotope incorporation into the RNA of irradiated cells,[40] and the rate at which precursors are incorporated into proteins seems similarly unaffected.[45]

The work of Dale,[13] Barron,[7] Forssberg,[23] and others on the irradiation of purified enzymes in dilute solutions suggested that certain enzymes, particularly those bearing active sulfhydryl groups, were extremely sensitive to rather small doses of radiation, well within the range of usual biologic interest. There is however little evidence that enzymes as they occur within the cell are similarly radiosensitive.[78] The mammalian cell is of course not a simple dilute solution or suspension, but an extremely complex colloidal system within which certain classes of enzymes seem to be confined within sub-structures such as the mitochondria, rather than uniformly dispersed. Moreover, great caution must be exercised in interpreting apparent changes in enzyme activity of irradiated tissues.[21] For example, the observation by several groups[2,15,18,84] that the activity of certain enzymes of highly radiosensitive tissues such as spleen increases strikingly several days after irradiation is more conservatively interpreted as reflecting a change in cell population, due to selective destruction of the more radiosensitive cellular elements, rather than a reflection of a real change in enzyme activity.

In closing this section, we may ask: what has modern radiobiologic research contributed to our understanding of the reasons for the differential radiosensitivity of different classes of cells and tumors? For normal tissues, we now understand that such differences may in part be unreal; that is to say, tissues which seem radioresistant may really have suffered essentially the same injury as the more radiosensitive tissues but they have such an extremely low rate of cell division, and their individual cells have such a long life span, that the morphologic manifestation of the injury is almost indefinitely deferred, thus seeming not to have occurred at all. In contrast, the rapidly dividing tissues must reveal their injury very quickly. This is simply another way of looking at that portion of the old "law" of Bergonié and Tribondeau which holds that radiosensitivity is directly correlated with mitotic rate.

Another part of the "law," which states that radiosensitivity is inversely related to the degree of maturation or differentiation of the cell, has long been known to abound in paradoxes and exceptions, such as the fact that the mature small lymphocyte is far more radiosensitive than its immature stem cell precursors. Another such exception has now been pointed out by Hicks *et al.*[39] who found that the differentiating, presumably postmitotic neuroblast of the embryonic brain is more radiosensitive than the intensely mitotically active primitive cell layer from which it originates.

Differences in mitotic rate and in degree of differentiation certainly do not provide an adequate explanation for the tremendous differences in radiosensitivity exhibited by different types of tumors. Even though it is generally true that the more rapidly dividing and more undifferentiated tumors tend to be more radiosensitive, it is nonetheless also true that two different tumors, both growing at essentially the same rate and having roughly the same degree of differentiation, may be poles apart in their response to radiation.[26] Rapidly growing, anaplastic malignant melanomas or thyroid carcinomas tend to be highly radioresistant, whereas undifferentiated epidermoid carcinomas are usually quite radiosensitive. Numerous other examples readily come to mind. No satisfactory clinical or laboratory explanation for this aspect of differential radiosensitivity has yet emerged. Here perhaps lies one of the greatest challenges to the radiobiologist.

B. EFFECTS ON THE ENVIRONMENT

The importance of radiation effects on the tumor bed has been clearly stated by Shields Warren:[95] "After the usual dose of radiation there is partial or complete recovery of some of the tumor cells and, were it not for the concomitant effects produced on the connective tissue stroma and blood vessels, no lasting effect on an irradiated part would be noted."

Merwin, Algire, and Kaplan[65] made direct microscopic observations of the radiation response of tumor blood vessels in transparent chambers in mice. Initial tumor regression resulting from doses of 2,000 to 5,000 r was followed by recurrent growth from one or more viable foci. However, the irradiated vascular endothelium had become incapable of budding new capillaries to keep pace with the growth of the recurrent tumor nodules, which rapidly outstripped their blood supply and underwent late necrosis on the basis of pressure ischemia. When the bed was pre-irradiated, it failed to provide the usual prompt vascular response for the subsequently introduced tumor. These observations, indicating that radiation injury sustained by the capillary endothelial buds plays an important role in tumor therapy, have been extended recently by Merwin and Hill.[66]

Clinical radiotherapists have long been aware of the tendency for tumors in a densely scarred or otherwise ischemic region to be more radioresistant than the same histologic variety of neoplasm would otherwise be. Recurrences of tumors often spring from the margins of necrotic zones. Moreover, Schwarz in 1909 noted that ischemia induced by pressure on the skin could reduce the intensity of the cutaneous erythema reaction.

All of these clinical observations point to the oxygen content of the blood, and that within the tumor cells themselves, as an important factor in radiosensitivity. This phenomenon has now been rediscovered in experimental radiobiology. Many species of microorganisms, plants, and several solid tumors of mice have been shown to exhibit a distinct oxygen dependence in their response to radiations of low specific ionization. However, it was not until recent years that Gray and his associates[32,33] clearly expounded the potential therapeutic implications of the oxygen effect. They reasoned that since many tumors tend to outgrow their blood supply, nests of anoxic, relatively radioresistant cells might persist and ultimately lead to tumor recurrence. Added support for this concept came from the careful histopathologic studies of irradi-

ated human tumors by Thomlinson and Gray.[91]

Procedures designed to increase blood oxygen content of tumor-bearing patients would be expected to alter oxygen concentration most effectively in initially anoxic cells, and might thus contribute selectively to tumor eradication. Clinical experiments to this end have now been initiated in Sweden by Hultborn and Forssberg[48] who irradiated patients while they were breathing oxygen at ordinary atmospheric pressure, with some suggestion of an enhanced clinical response, and in London by Churchill-Davidson and his colleagues[12] who have irradiated patients with far-advanced cancers in a pressure chamber under three atmospheres of oxygen. Although practical difficulties prevented controlled observations on similar patients breathing air under normal pressure, their preliminary results are nonetheless intriguing in a few extremely far advanced cases. This work has now captured the interest of a number of other radiotherapeutic groups in several countries, and it is likely that more carefully controlled trials will be forthcoming in the near future. The practical clinical difficulties attending high pressure oxygen therapy are so serious, however, that it seems unlikely that this technique can ever be extended to any large fraction of patients referred for radiotherapy.

In connection with the oxygen effect, it seems pertinent to mention briefly the extensive experimentation which has now been performed with a number of pharmacologic agents such as cysteine,[75] glutathione,[10] beta-mercaptoethylamine,[5] and related compounds,[4] all of which seem to reduce the effect of a given dose of radiation if given very shortly before radiation exposure. It was at first thought that these "pre-protective" agents might selectively affect different types of tissues, but no such differential effect has yet been observed.[88,89] The preponderance of evidence now suggests that much if not all of the effect exerted by these agents results from their capacity to bind oxygen, and thus to lower the effective intracellular oxygen concentration.

The influence of nutrition on the radiosensitivity of tissues and tumors has received little experimental attention. Working with the transplanted Walker rat carcinoma, Elson and Lamerton[19] found that initial regressions induced by irradiation were essentially similar regardless of protein intake, but the tumors tended to recur and "escape," going on to kill the host with greater frequency in protein-deficient animals than in animals on adequate protein intake. These observations were extended by Devik *et al.*[14] who, in studying sections of the irradiated tumors from both series of rats, had the impression that the macrophage and stromal defense reaction was appreciably less intense in the protein-deficient animals than in the high protein group. In the latter, this stromal reaction tended to wall off and trap small pockets of radiation-injured but potentially viable tumor cells, leading to their ultimate disappearance, possibly by interference with the blood supply. In contrast, the stromal reaction evoked in the protein-deficient animals was meagre and seemed to present a very inadequate barrier to the recovery and proliferation of radiation-injured tumor cells. These observations are of considerable potential interest at a clinical level, but should be re-studied and confirmed with spontaneous tumors irradiated *in situ* in the original host, since immunologic reactions between the transplanted tumor and its host, possibly augmented by radiation-induced necrosis, may have accounted for at least part of the observed results.

Other morphologic observations on the role of the stromal defense reaction in supplying the "coup de grace" to radiation-damaged tumors have been described by Jolles and Koller[49] and by Glucksmann.[29] Such observations on serial biopsy material are difficult to measure, however; a reproducible, quantitative laboratory technique

for studying the connective tissue contribution to the radiation response of tumors is urgently needed.

C. EFFECTS RELATED TO THE NATURE AND MODE OF APPLICATION OF THE AGENT

The pioneering studies of Regaud and his colleagues revealed that fractionated doses of radiation, unlike single large doses, could abolish spermatogenesis in the rabbit without producing necrosis of the overlying scrotal epidermis. This experimental milestone was applied clinically by Coutard, whose results in the treatment of epidermoid carcinomas of the head and neck were so far superior to those previously recorded that they revolutionized clinical radiotherapy. Today, virtually all radiotherapists follow a more or less prescribed program of dose fractionation, based in large part on rather limited empirical data compiled by Strandqvist. These and other time-dose data have now been subjected to a searching scrutiny by Andrews and Moody,[1] and by du Sault.[17]

Even if the Strandqvist curves were valid for a particular tumor, there is no reason to believe that different varieties of neoplasms would all exhibit the same curve. This general question therefore deserves vigorous experimental and clinical investigation. Experimental attention has recently turned to a technique originally developed by Quimby and MacComb[82] in a clinical study of the effect of two-dose fractionation on the cutaneous erythema reaction. A refined experimental application of this split-dose technique has now been employed by Paterson, Gilbert and Haigh[72] in a study of radiation recovery times in monkeys, and in other experimental investigations by Kohn and Kallman[61] and by Mole.[69] This simple quantitative approach should now be applied to the study of recovery characteristics of a spectrum of tumors. Although such studies are appreciably more difficult under clinical conditions than they would be in the experimental laboratory, the work of Sambrook *et al.*[84] and of Constance Wood and Boag[97] indicates that some of the difficulties may be overcome by the exercise of a little ingenuity.

Most clinical radiotherapy is conducted with roentgen-ray beams having peak energies in the 200 kv. range. The recent availability of a variety of supervoltage sources has focused interest on the question of whether the relative biologic effectiveness (RBE) of such beams differs significantly from that of the standard 200 kv. roentgen-ray beam. Although earlier work[25,35,36,66,76,77] indicated that the RBE of roentgen rays generated at supervoltage energies was only about 0.6 to 0.8 with reference to 200 kv. roentgen rays, recent workers in this field have stressed the importance of making the dosimetry of the two beams comparable in terms of absorbed energy at the tissue level where the biologic effect is measured. It seems likely that in the earlier comparisons dosimetric inequalities were not eliminated. More precise recent studies have yielded appreciably higher values, ranging from about 0.85 to 1.0, for the RBE of supervoltage roentgen rays generated at from 1 to 24 mev., as compared with 200 kv. roentgen rays, measured with various biologic endpoints.[34,56,57,58,59,60,64] As a rough approximation, therefore, there is probably no more than a 10 per cent difference in RBE between supervoltage and 200 kv. roentgen rays; such a small difference would be difficult to detect clinically, as Fletcher has noted.[22] Any advantages that supervoltage beams might have over conventional roentgen rays therefore clearly depend upon the improved distribution of radiant energy within the volume of the tumor, as compared with that delivered to the other tissues of the patient. There has not yet been any conclusive demonstration that supervoltage therapy yields a significantly improved cure rate for any particular variety of cancer. The accumulation of convincing data to settle this question will probably require a cooperative randomized clinical trial. The practical clinical advan-

tages of supervoltage therapy, in terms of enhanced patient comfort, minimal skin reaction, decreased integral dose, and greater uniformity of dose distribution have, of course, been immediately apparent to all of those who have had the opportunity to work with such devices.

The contribution of whole body radiation to tumor response has been experimentally investigated only in recent years, when Hollcroft *et al.*[41,42] showed that both initial regressions and the proportion of permanent cures of a transplantable mouse lymphosarcoma were appreciably greater when a combination of local tumor irradiation and whole body irradiation (with the tumor shielded) was employed. This is an extremely interesting observation which should be studied with other types of tumors as well. More recently, Barnes *et al.*[6] and Trentin[92] have utilized lethal doses of whole body irradiation to eradicate leukemia in mice, preventing radiation death by the intravenous injection of exogenous bone marrow after exposure. The frequency with which late deaths occur in heavily irradiated mice temporarily kept alive with foreign bone marrow and the frequency of other late injuries such as cataracts would seem to preclude the practical application of this approach in the treatment of human leukemia, although at least one instance in which the bone marrow of an identical twin was employed to sustain life in a child massively irradiated for acute leukemia has already been reported in the public press.

Finally, we may turn our attention to the use of "sensitizers," a miscellaneous class of pharmacologic agents having no direct effect on a tumor by themselves, but thought to have a potentiating effect on the response of that tumor to a given dose of radiation. Although a number of such compounds has now been investigated,[11,62,64,65,81] no conclusive evidence of true potentiating action has yet appeared. The encouraging preliminary clinical and experimental observations reported with some agents have not been sustained in more rigorous experimental trials.[55]

The rapid expansion of cancer chemotherapy has attracted the interest of radiotherapists to the possibility that combined treatment of tumors with chemotherapeutic agents and radiation might in some instances yield enhanced results.[90] The only well-defined clinical situation in which such combined therapy has been claimed to be effective is in the treatment of retinoblastoma with a combination of radiation and triethylene-melamine.[83] Very recently, Kligerman and Shapiro[54] have reported encouraging, though highly preliminary, results in the treatment of transplantable mouse mammary tumor 755 with radiation and multiple combination chemotherapy, aimed largely at the energy metabolism of the tumor cell. This type of investigation seems of sufficient interest to warrant extension to other types of spontaneous and induced tumors, treated in the hosts of origin.

Stanford University
School of Medicine
Clay and Webster Streets
San Francisco 15, California

REFERENCES

1. Andrews, J. R., and Moody, J. M. Dose-time relationship in radiotherapy. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1956, *75*, 590–596.
2. Ashwell, G., and Hickman, J. Effect of x-irradiation upon enzyme systems of mouse spleen. *Proc. Soc. Exper. Biol. & Med.*, 1952, *80*, 407–410.
3. Avery, O. T., MacLeod, C. M., and McCarty, M. Studies on chemical nature of substance inducing transformation of pneumococcal types: Induction of transformation by a desoxyribonucleic acid fraction isolated from Pneumococcus type III. *J. Exp. Med.*, 1944, *79*, 137–158.
4. Bacq, Z. M., Herve, A., Lecomte, J., and Fisher, P. Cyanide protection against x-irradiation. *Science*, 1950, *111*, 356–357.
5. Bacq, Z. M., Dechamps, G., Fischer, P., Herve, A., Le Bihan, J., Lecomte, J., Pirotte, M., and Rayet, P. Protection against x-rays and therapy of radiation sickness with β-mercaptoethylamine. *Science*, 1953, *117*, 633–636.
6. Barnes, D. W., Corp, M. J., Loutit, J. F., and Neal, F. E. Treatment of murine leukemia with x-rays and homologous bone marrow;

preliminary report. *Brit. Med. J.*, 1956, *2*, 626–628.

7. BARRON, E. S. G. Effect of ionizing radiations on sulfhydryl systems. *In*: Biological Antioxidants. Josiah Macy, Jr. Foundation, New York, 1951 (pp. 81–115).
8. BLOOM, W., and BLOOM, M. A. Histological changes after irradiation. *In:* Radiation Biology, A. Hollaender, Editor. McGraw-Hill Book Co., Inc., New York, 1954. Vol. I, part II, Chap. 17, pp. 1091–1143.
9. CARLSON, J. G. Immediate effects on division, morphology, and viability of the cell. *In:* Radiation Biology, A. Hollaender, Editor. McGraw-Hill Book Co., Inc., New York, 1954. Vol. I, part II, Chap. 11, pp. 763–824.
10. CHAPMAN, W. H., and CRONKITE, E. P. Further studies of beneficial effect of glutathione on x-irradiated mice. *Proc. Soc. Exper. Biol. & Med.*, 1950, *15*, 318–322.
11. CARPENDER, J. W. J., and LANIER, R. R. Combined effect of tumor inhibitor (5-amino-7-hydroxy-1 H-V-triazolo(d) pyrimidine) and x-ray therapy. *Radiology*, 1950, *55*, 874–878.
12. CHURCHILL-DAVIDSON, I., SANGER, C., and THOMLINSON, R. H. Oxygenation in radiotherapy. II. Clinical application. *Brit. J. Radiol.*, 1957, *30*, 406–422.
13. DALE, W. M. Action of radiation on aqueous solutions; experimental work with enzymes in solution. *Brit. J. Radiol.*, 1947, Suppl. 1, 46–49.
14. DEVIK, F., ELSON, L. A., KOLLER, P. C., and LAMERTON, L. F. Influence of diet on Walker rat carcinoma 256, and its response to x-radiation; cytological and histological observations. *Brit. J. Cancer*, 1950, *4*, 298–314.
15. DUBOIS, K. P., and PETERSEN, D. F. Adenosine triphosphatase and 5-nucleotidase activity of hematopoietic tissues of irradiated animals. *Am. J. Physiol.*, 1954, *176*, 282–286.
16. DURYEE, W. R. Nature of radiation injury to amphibian cell nuclei. *J. Nat. Cancer Inst.*, 1949, *10*, 735–795.
17. DU SAULT, L. A. Time-dose relationships. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1956, *75*, 597–606.
18. EICHEL, H. J. Effect of x-irradiation on purine-metabolizing enzymes of rat liver and spleen. *Proc. Soc. Exper. Biol. & Med.*, 1955, *88*, 155–158.
19. ELSON, L. A., and LAMERTON, L. F. Influence of protein content of diet on response of Walker rat carcinoma 256 to x-radiation. *Brit. J. Cancer*, 1949, *3*, 414–426.
20. FAILLA, G. Some aspects of the biological action of ionizing radiations. AM. J. ROENTGENOL. & RAD. THERAPY, 1940, *44*, 649–664.
21. FEINSTEIN, R. N. Interpretation of some enzyme activity increases after whole body x-irradiation. *Radiation Research*, 1956, *4*, 217–220.
22. FLETCHER, G. H. Clinical program to evaluate practical significance of higher energy levels than the 1–3 mev. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1956, *76*, 866–893.
23. FORSSBERG, A. Action of roentgen rays on enzyme catalase. *Acta radiol.*, 1946, *27*, 281–293.
24. FRIEDENWALD, J. S., and SIGELMAN, S. Influence of ionizing radiation on mitotic activity in rat's corneal epithelium. *Exper. Cell Research*, 1953, *4*, 1–31.
25. FULLER, J. B., CHEN, I., LAUGHLIN, J. S., and HARVEY, R. A. Comparison of biological effects of whole-body irradiation with 22.5-Mev x-rays, 18-Mev electrons, and 400-Kev x-rays in rat. *Radiation Research*, 1955, *3*, 423–434.
26. GOLDFEDER, A. Further studies on relation between radiation effects, cell viability, and induced resistance to malignant growth. IV. Comparison of effects of roentgen rays on mammary tumors autogenous to inbred strains of mice (dba and C3H). *Radiology*, 1947, *49*, 724–732.
27. GLUCKSMANN, A. Quantitative histological analysis of radiation effects in human carcinomata. *Brit. Med. Bull.*, 1946, *4*, 26–30.
28. GLUCKSMANN, A. Influence of systemic factors on differentiation and radiocurability of cervical cancers. *Brit. J. Radiol.*, 1956, *29*, 483–487.
29. GLUCKSMANN, A. Role of tumor bed in treatment of squamous-cell cancers by irradiation. *J. Obst. & Gynaec. Brit. Empire*, 1950, *57*, 322–327.
30. GRAY, L. H. Some characteristics of biological damage produced by ionizing radiations. *Radiation Research*, 1954, *1*, 189–213.
31. GRAY, L. H. Initiation and development of cellular damage by ionizing radiation. *Brit. J. Radiol.*, 1953, *26*, 609–618.
32. GRAY, L. H. Oxygenation in radiotherapy. I. Radiobiological considerations. *Brit. J. Radiol.*, 1957, *30*, 403–406.
33. GRAY, L. H., CONGER, A. D., EBERT, M., HORNSBY, S., and SCOTT, O. C. A. Concentration of oxygen dissolved in tissues at time of irradiation as a factor in radiotherapy. *Brit. J. Radiol.*, 1953, *26*, 638–648.
34. GUNTER, S. E., KOHN, H. I., TYREE, E. B., LAUGHLIN, J., OVADIA, J., SHAPIRO, G., and THOMPSON, P. Relative biological effectiveness of 180-Kevp and 22.5-Mevp x-rays determined from the dose-survival curves of *Saccharomyces cerevisiae*. *Radiation Research*, 1956, *4*, 326–338.
35. HAAS, L. L., HARVEY, R. A., and LAUGHLIN, J. S. Biological evaluation of skin effects of the 23 mev. betatron. AM. J. ROENTGENOL.,

Rad. Therapy & Nuclear Med., 1952, *58*, 644–653.

36. Haas, L. L., Laughlin, J. S., and Harvey, R. A. Biological effectiveness of high-speed electron beam in man. *Radiology*, 1954, *62*, 845–850.
37. Harrington, H., and Lavik, P. S. Study of direct and indirect effects of irradiation on P^{32} incorporation by Ehrlich ascites tumor cells *in vivo* and *in vitro*. *Cancer Research*, 1957, *17*, 38–42.
38. Hevesy, G. On effect of roentgen rays on cellular division. *Rev. Modern Physics*, 1945, *17*, 102–111.
39. Hicks, S. P., Brown, B. L., and D'Amato, C. J. Regeneration and malformation in nervous system, eye, and mesenchyme of the mammalian embryo after radiation injury. *Am. J. Pathology*, 1957, *33*, 459–481.
40. Hokin, M. R., and Hokin, L. E. Protein synthesis and ribonucleic acid metabolism in mouse pancreas *in vitro* after whole body irradiation with x-rays. *J. Biol. Chem.*, 1956, *219*, 85–94.
41. Hollcroft, J. W., Lorenz, E., and Mathews, M. Factors modifying the effect of x-irradiation on regression of transplanted lymphosarcoma. *J. Nat. Cancer Inst.*, 1952, *12*, 751–763.
42. Hollcroft, J. W., and Mathews, M. Effects of ionizing irradiation treatments on tumor regression. *J. Nat. Cancer Inst.*, 1953, *14*, 527–535.
43. Holmes, B. E. Inhibition of ribo- and thymonucleic acid synthesis in tumour tissue by irradiation with x-rays. *Brit. J. Radiol.*, 1947, *20*, 450–453.
44. Holmes, B. E., and Mee, L. K. Inhibition of DNA synthesis by irradiation with special reference to irradiation in the early stages of liver regeneration. *In:* Radiobiology Symposium, Z. M. Bacq and P. Alexander, Editors. Academic Press, New York, 1954, pp. 220–229.
45. Holmes, B. E., and Mee, L. K. Incorporation of methionine-S^{35} into proteins of Jensen rat sarcoma cells after irradiation of tumour. *Brit. J. Radiol.*, 1952, *25*, 273–278.
46. Hotchkiss, R. D. Biological role of deoxypentose nucleic acids. *In:* The Nucleic Acids, E. Chargaff and J. N. Davidson, Editors. Academic Press, Inc., New York, 1955. Vol. II, Chap. 27, pp. 435–473.
47. Howard, A., and Pelc, S. R. Synthesis of DNA in normal and irradiated cells and its relation to chromosome breakage. *Heredity*, 1952, Suppl. *6*, 261–273.
48. Hultborn, K. A., and Forssberg, A. Irradiation of skin tumours during pure oxygen inhalation. *Acta radiol.*, 1954, *42*, 475–484.
49. Jolles, B., and Koller, P. C. Role of connective tissue in radiation reaction of tumours. *Brit. J. Cancer*, 1950, *4*, 77–89.
50. Kaplan, H. S. Radiation research and future of radiotherapy. *Radiology*, 1957, *69*, 801–808.
51. Kaufmann, B. P. Chromosome aberrations induced in animal cells by ionizing radiations. *In:* Radiation Biology, A. Hollaender, Editor. McGraw-Hill Book Co., Inc., New York, 1954. Vol. I, part II, Chap. 9, pp. 627–711.
52. Kelly, L. S., Hirsch, J. D., Beach, G., and Palmer, W. Time function of P^{32} incorporation into DNA of regenerating liver; effect of irradiation. *Cancer Research*, 1957, *17*, 117–121.
53. Klein, G., and Forssberg, A. Studies on effect of x-rays on biochemistry and cellular composition of ascites tumors. I. Effect on growth rate, cell volume, nucleic acid and nitrogen content in the Ehrlich ascites tumor. *Exper. Cell Research*, 1954, *6*, 211–220.
54. Kligerman, M. M., and Shapiro, D. M. Augmentation of radiotherapeutic effect by cancer chemotherapy. *Radiology*, 1957, *69*, 194–199.
55. Kohn, H. I., and Gunter, S. E. Effect of menadiol diphosphate (Synkavite) on the sensitivity of *E. coli* and *S. cerevisiae* to x-rays. *Radiation Research*, 1955, *2*, 351–353.
56. Kohn, H. I., and Gunter, S. E. Relative biological efficiency of 1000-Kvp and 250-Kvcp x-rays. I. General introduction. Determinations based on dose-survival curves of *Saccharomyces cerevisiae*, haploid and diploid. *Radiation Research*, 1956, *5*, 674–687.
57. Kohn, H. I., and Gunter, S. E. Relative biological efficiency of 1000-Kvp and 250 Kvcp x-rays. II. Supplemental determinations based on dose-survival curves of *Escherichia coli* and *Rhodopseudomonas spheroides*. *Radiation Research*, 1956, *5*, 688–692.
58. Kohn, H. I., and Kallman, R. F. Relative biological efficiency of 1000-Kvp and 250-Kvcp x-rays. III. Determinations based on $LD_{50/28}$ and killing time of the mouse. *Radiation Research*, 1956, *5*, 693–699.
59. Kohn, H. I., and Kallman, R. F. Relative biological efficiency of 1000-Kvp and 250 Kvcp x-rays. IV. Determinations based on dose-response curves for testicular weight in mouse. *Radiation Research*, 1956, *5*, 700–709.
60. Kohn, H. I., and Kallman, R. F. Relative biological efficiency of 1000-Kvp and 250 Kvcp x-rays. V. Determinations based on LD_{50} of 4-day-old chick embryo. *Radiation Research*, 1956, *5*, 710–714.
61. Kohn, H. I., and Kallman, R. F. Influence of strain on acute x-ray lethality in mouse. II. Recovery rate studies. *Radiation Research*, 1957, *6*, 329–338.
62. Mack, H. P., Diehl, W. K., Peck, G. C., and Figge, F. H. J. Evaluation of combined effects

of hematoporphyrin and radiation. I. Treatment of carcinoma of cervix. *Cancer*, 1957, *10*, 529–539.

63. Mazia, D. Relation of morphology of cell to its functional behavior following irradiation. *In:* Cellular Aspects of Basic Mechanisms in Radiobiology, H. M. Patt and E. L. Powers, Editors. National Academy of Sciences-National Research Council Publication #450, Washington, D.C., 1956, page 145.
64. Medical Research Council Unit, Christie Hospital and Holt Radium Institute. Relative biological efficiency of 4 MeV and 300 Kv radiations. *Brit. J. Radiol.*, 1957, *30*, 337–355.
65. Merwin, R. M., Algire, G. H., and Kaplan, H. S. Transparent chamber observations of response of a transplantable mouse mammary tumor to local roentgen irradiation. *J. Nat. Cancer Inst.*, 1950, *11*, 593–623.
66. Merwin, R. M., and Hill, E. L. Effect of local roentgen irradiation on formation of new capillaries after injury. *J. Nat. Cancer Inst.* 1955, *15*, 1031–1037.
67. Mitchell, J. S. Clinical trials of tetra-sodium 2-methyl-1:4-naphtho-hydroquinone diphosphate, in conjunction with x-ray therapy. *Brit. J. Cancer*, 1948, *2*, 351–359.
68. Mitchell, J. S. Clinical assessment of tetra-sodium 2-methyl-1:4-naphtho-hydroquinone diphosphate as radiosensitizer in radiotherapy of malignant tumors. *Brit. J. Cancer*, 1953, *7*, 313–328.
69. Mole, R. H. Quantitative observations on recovery from whole body irradiation in mice. II. Recovery during and after daily irradiation. *Brit. J. Radiol.*, 1957, *30*, 40–46.
70. Moos, W. S., Fuller, J. B., Henderson, W. J., Dallenbach, F., and Harvey, R. A. Lethal effects on rats of single and multiple exposures of 400-Kv and 22-Mv x-irradiation. *Radiation Research*, 1955, *3*, 44–51.
71. Ord, M. G., and Stocken, L. A. Effects of x- and γ-radiation on nucleic acid metabolism in rat *in vivo* and *in vitro*. *Biochem. J.*, 1956, *63*, 3–8.
72. Paterson, E., Gilbert, C. W., and Haigh, M. V. Effect of paired doses of whole body irradiation in rhesus monkey. *Brit. J. Radiol.*, 1956, *29*, 218–226.
73. Patt, H. M. Factors in radiosensitivity of mammalian cells. *Ann. New York Acad. Sci.*, 1955, *59*, 649–664.
74. Patt, H. M., and Powers, E. L. Cellular Aspects of Basic Mechanisms in Radiology. National Academy of Sciences-National Research Council Publication #450, Washington, D.C., 1956.
75. Patt, H. M., Tyree, E. B., Straube, R. L., and Smith, D. E. Cysteine protection against x-irradiation. *Science*, 1949, *110*, 213–214.
76. Pelc, S. R., and Howard, A. Effect of various doses of x-rays on number of cells synthesizing deoxyribonucleic acid. *Radiation Research*, 1955, *3*, 135–142.
77. Potter, V. R., van Lancker, J., and Beltz, R. E. X-ray inhibition of DNA biosynthesis. *Proc. Am. Ass'n. Cancer Research*, 1956, *2*, 140.
78. Powell, W. F., and Pollard, E. Radiation inactivation of enzymes inside and outside intact cells. *Radiation Research*, 1955, *2*, 109–118.
79. Puck, T. T., and Marcus, P. I. Action of x-rays on mammalian cells. *J. Exper. Med.*, 1956, *103*, 653–666.
80. Quastler, H. Biologic effects of high energy roentgen rays. *Acta Union Internat. contra Cancrum.*, 1949, *6*, 825–830.
81. Quastler, H., and Clark, R. K. Biological evaluations of 20 million volt roentgen rays. I. Acute roentgen death in mice. Am. J. Roentgenol. & Rad. Therapy, 1945, *54*, 723–727.
82. Quimby, E. H., and MacComb, W. S. Further studies on rate of recovery of human skin from effects of roentgen- or gamma-ray irradiation. *Radiology*, 1937, *29*, 305–312.
83. Reese, A. B., Hyman, G. A., Merriam, G. R., Jr., Forrest, A. W., and Kligerman, M. M. Treatment of retinoblastoma by radiation and triethylenemelamine. *Arch. Ophthalmol.*, 1955, *53*, 505–513.
84. Sambrook, D. K., Thackray, A. C., and Woodyatt, P. B. Comparative study of radiotherapy techniques. *Brit. J. Cancer*, 1950, *4*, 63–76.
85. Schwartz, S., Absolon, K., and Vermund, H. Some relationships of porphyrins, x-ray, and tumors. *Univ. Minnesota Med. Bull.*, 1955, *27*, 7–13.
86. Siminovitch, L., and Graham, A. F. Significance of ribonucleic acid and deoxyribonucleic acid turnover studies. *J. Histochem. & Cytochem.*, 1956, *4*, 508–515.
87. Sinsheimer, R. L. First steps toward a genetic chemistry. *Science*, 1957, *125*, 1123–1128.
88. Storaasli, J. P., Rosenberg, S. A., and Friedell, H. L. Effect of cysteine on radiosensitivity of rat lymphosarcoma. *Cancer*, 1953, *6*, 1244–1247.
89. Straube, R. L., Patt, H. M., Smith, D. E., and Tyree, E. B. Influence of cysteine on the radiosensitivity of Walker rat carcinoma 256. *Cancer Research*, 1950, *10*, 243–244.
90. Thomas, S. F. Combined therapy; radiation and chemicals. *Radiology*, 1957, *69*, 204–207.
91. Thomlinson, R. H., and Gray, L. H. Histological structure of some human lung cancers and possible implications for radiotherapy. *Brit. J. Cancer*, 1955, *9*, 539–549.
92. Trentin, J. J. Whole-body x-ray and bone marrow therapy of leukemia in mice. *Proc.*

Am. Ass'n. Cancer Research, 1957, *2*, 256 (abstr.).

93. Uretz, R. B., Bloom, W., and Zirkle, R. E. Irradiation of parts of individual cells. II. Effects of an ultraviolet microbeam focused on parts of chromosomes. *Science*, 1954, *120*, 197–199.
94. Uyeki, E. M. Effect of x-irradiation on rat spleen adenylate kinase activity. *Fed. Proc.*, 1955, *14*, 295.
95. Warren, S. Mechanism of radiation effects against malignant tumors. *J.A.M.A.*, 1947, *133*, 462–463.
96. Whitehead, R. W., and Lanier, R. R. Combined effect of a halogenated urethan derivative and x-rays on growth of certain experimental tumors. *Cancer Research*, 1954, *14*, 418–422.
97. Wood, C. A. P., and Boag, J. W. Researches on radiotherapy of oral cancer. *Med. Research Council*, Special Report Series, #267, 1950.
98. Zamenhof, S., Alexander, H. E., and Leidy, G. Biological activity of nucleic acids. *Canad. J. Med. Sci.*, 1953, *31*, 252–262.
99. Zirkle, R. E., and Bloom, W. Irradiation of parts of individual cells. *Science*, 1953, *117*, 487–493.

VOL. 80, NO. 5

TUMOR RESPONSE TO IONIZING RAYS AT ELEVATED TEMPERATURES†

A REVIEW AND DISCUSSION

By OLEG S. SELAWRY, M.D., JAMES C. CARLSON, M.S., *and* GEORGE E. MOORE, M.D., PH.D.
BUFFALO, NEW YORK

"We are making no claims as to the cure of these patients that have had combined fever and x-ray therapy, but we do feel that their lives have been prolonged in comfort in a majority of cases," L. D. Scott.[64]

INTEREST in the combined effect of heat and ionizing radiation arose from the desire to secure more pronounced roentgen ray effects in "radioresistant" or in poorly accessible tumors. Since there is no review on this subject, a general discussion seems timely.

PROCEDURES

The effect of ionizing radiations at elevated temperatures had been studied on experimental and spontaneous tumors in animals, in man and in tissue cultures. Roentgen rays* and, less frequently, radium[32,42,71] have been utilized for the production of ionizing radiation. The dosages applied were usually given in roentgens to the skin, in minutes exposure time, or in per cent skin erythema dose. Occasionally, no information was given about the dosage. Heat was applied mostly by short waves (SW) for ten to twenty minutes, less frequently by water,[1,11,25,76,81] air,[16,42,74] and ultrasound (US).[18,19,61,76–80] In the latter case it is claimed that hyperthermia and mechanical agitation both contribute to the observed effects. The temperatures were measured in the surrounding medium (air, water), sometimes in the treated animal (rectal temperature), and rarely in the tumor. In most experiments involving short waves, exact temperature measurements have not been described.

Birkner and Wachsmann,[8] however, did determine the temperature in a carcinoma of the skin during short wave treatment. Using a quartz-benzole thermometer he found inhomogeneous temperature distribution throughout the tumor with a maximum temperature of about 44°C. In order to investigate the possibility of treating deep seated tumors, Gruner[25] employed short wave therapy to a normal esophagus obtaining a maximum temperature of 39°C. The heat applied (as given in degrees centigrade and duration of exposure time) can only be estimated. In most tumors it is estimated that temperatures between 38 and 42°C. may have been reached for ten to twenty minutes of short wave treatment depending upon the wavelength, power, type of short wave, and the site of the tumor.[17,52,57,58,61] In cases where hyperthermia was induced by a waterbath[11,39] or hot air,[16,72] rectal temperatures between 40°C. and 42°C. were maintained for up to five hours. In most cases several combined treatments were applied.

Heat and roentgen irradiation have been given simultaneously[32,76–80] as well as in every possible sequence: heat first,[2,8,20–24,64,67–69,75] simultaneously and afterwards,[10,45,46] before and after irradiation,[45,46] following irradiation[37] and, finally, between two sessions of irradiation.[56]

RESULTS REPORTED

The efficacy of combined treatment can be evaluated from the reaction of the tumor of the surrounding tissues, and the general condition of the host.

* When the references include a large segment of the bibliography, they will not be mentioned specifically.

† From the Department of Experimental Biology, Roswell Park Memorial Institute, Buffalo, New York.
This review was supported in part by the PHS Grant No. C-2830 and the Lichtenfels-Speidel-Willard Grant.

Effect on Tumor Growth—Human. As early as 1910, Müller[45,46] combined roentgen rays and diathermy in the treatment of cancer patients. In 1912 he reported on 100 patients with advanced, histologically confirmed cancer of various sites such as breast, bronchus, esophagus and stomach. Of these tumors, 32 per cent regressed completely, including 2 originally "radioresistant" tumor, 36 per cent regressed temporarily and faster than could be expected of lesions treated with roentgen rays only, and 32 per cent progressed as much as those treated with roentgen irradiation alone. The effectiveness of the combined treatment was evaluated on the basis of the personal experience of the investigator rather than on a comparative series. The follow-up time was two years or less and no temperature measurements were given.

Müller's publications were followed by thirty-three other papers which included 500 more patients. However, the treatment conditions were too heterogenous and the technical data were insufficient to permit intercomparison of the results. The patients were followed for three to eighteen months,[2,16,20,32,78] sometimes for two or more years[45,46,64,74] and in certain papers no follow-up time was given.

Most authors selected either far advanced or previously unsuccessfully irradiated tumors. Shoulders and co-workers[68] felt that sarcomas were more sensitive than carcinomas. These authors treated 67 carcinomas and 33 sarcomas. Thirty-three per cent of the former and 30 per cent of the latter regressed completely; 21 per cent and 45 per cent, respectively, regressed partially; 35 and 24 per cent, respectively, showed no response. The results of Müller[46] and others, however, showed no better results in sarcomas.

The following results were evaluated by clinical comparison: Korb[38] treated two basal cell carcinomas of the skin of the same patient with the roentgen ray dosage. One treatment, however, was combined with hyperthermia. At a given roentgen ray dosage, the tumor receiving radiation alone continued to grow, while the other lesion receiving combined treatment regressed completely. Fuchs[20–24] and Woeber[76–80] compared the roentgen ray dosage necessary to cause regression of skin cancer with and without combined treatment. Using equipment particularly designed for simultaneous application of ultrasound and roentgen rays, Woeber reduced the cancerocidal roentgen ray dose by as much as 45 per cent. In the reports of all other authors, the same roentgen ray dose was used that would have been applied when treating with radiation alone.

Fuchs[20–24] is the only author who described histologic findings after combined treatment in man. In 1 patient, who had been treated three months previously for bronchogenic carcinoma and who died from an embolus, no cancer was detectable. In others, only "relatively small tumor remnants, surrounded and encapsulated by connective tissue were found."

Effect on Experimental Tumors. As a result of inadequate data and experimental controls, clinical studies have failed to resolve many questions concerning the desirability of the combined treatments and the most effective mode of application. Some of these questions were answered by representative series of experiments in animals and tissue cultures. These studies were performed with mouse tumors (Ehrlich carcinoma, Crocker and Wood sarcoma), rat tumors (Walker carcinoma 256, Crocker and Jensen sarcoma) and rabbit tumors (Brown-Pearce tumor and Kato sarcoma). Comparative studies were also performed using normal tissues or healthy animals.[5,37,43,44,73]

All but one author[71] felt that the combined application of heat and roentgen rays was more effective than roentgen irradiation alone. Growth inhibition and tumor regression produced by a combination of temperatures and roentgen ray dosages that were by themselves ineffective, were observed by Mikawa,[43] Rohdenburg and Prime,[55] and Hill.[30] Mikawa

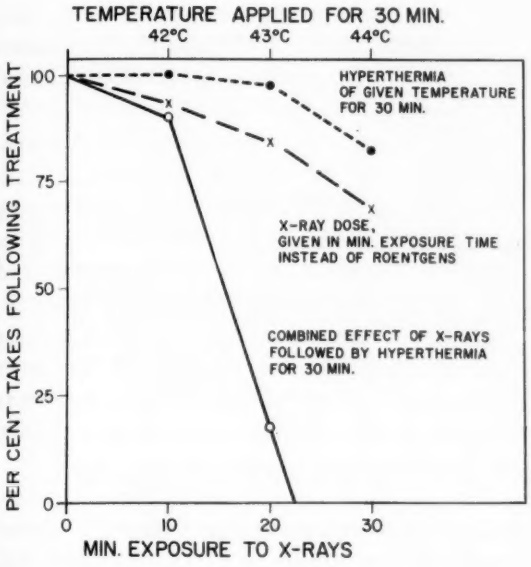

FIG. 1. Combined effect of heat and roentgen rays on tumor growth following data of Rohdenburg and Prime.[55]

studied Cochin embryos and rabbit fibroblasts, the latter in tissue cultures. Rohdenburg and Prime based their statements on experiments with 3,248 mice with Crocker sarcoma 180. These two authors immersed tumor particles weighing 2 to 3 mg. in Ringer's solution of various temperatures and exposed them to various roentgen ray doses before inoculating them subcutaneously into the host. Unexposed controls developed tumors in 98 per cent of 5,000 animals. Spontaneous regression of established tumors appeared in less than 1 per cent. The results were evaluated during a follow-up time of five weeks. As can be seen from Figure 1, based on Rohdenburg and Prime's results, the combined effect exceeded by far that of the summation of the two components at temperatures above 42°C. Corresponding results were found in spontaneous mammary tumors of the Lathrop mouse strain,[55] Jensen sarcoma[30] and an unidentified transplantable mouse tumor.[30]

Other authors combined partially effective roentgen ray doses with temperatures ineffective as such. An increase of effectiveness of 40 to 60 per cent was observed as judged by the cure rate in experimental tumors,[40] the sterilizing dose for rabbit testes,[6,37,40] the lethal dose for Ascaris eggs, and total body irradiation of young guinea pigs.[37,73]

Results with simultaneous or immediately subsequent application of heat and roentgen rays seemed to be superior to those obtained with hyperthermia followed later by irradiation,[2,20,21] although comparative studies on various sequences of heat and roentgen rays are incomplete. Some authors found no significant differences,[1,55,56] others found better effects when hyperthermia was preceded immediately by irradiation,[33,72] both *in vivo* and *in vitro*. Time intervals of twelve and twenty-four hours between hyperthermia and irradiation reduced the beneficial effects significantly.[33] In such time intervals, studies on 3,210 mice with Wood sarcomia indicated better results when hyperthermia was applied first (49.5 per cent cure rate as compared with 22.3 per cent).[48,49]

Woeber[76,77] felt that ultrasound was more effective than short waves or warm water for the combined treatment; he ascribed this to the mechanical component of ultrasound and showed pictures of aberrant chromosomes following ultrasound application to Walker carcinoma 256 in rats. Since the latter was observed also following heat treatment alone,[35] it is not specific for ultrasound. The use of ultrasound however, has undoubtedly certain advantages: temperature measurements can be obtained during the treatment,[18] the beams can be focused,[19] and simultaneous application with roentgen rays can be easily attained.[76,80]

Effect on Surrounding Tissues. The radiotherapist may be concerned with possible damage to the overlying skin during the heat treatment especially when warm water is employed. Yet, no author has mentioned permanent damage to the healthy tissue surrounding the lesion. Comparative studies in 8 volunteers were obtained by Woeber.[76] He observed a more pronounced primary erythema but lesser secondary erythema and not as much pigmentation at

corresponding sites following combined use of roentgen ray and ultrasound therapy. Sarasin[56] used infrared rays to reduce edema and radiation epidermitis following irradiation of carcinoma of the larynx. Birkner and Wachsmann[8] felt that the cosmetic effects in skin cancer were more satisfactory following the combined treatment. An observation by Barth[4] on increased injury to the skin in certain temperature ranges seems reasonable because of the increased hyperemia which leads to an increased response to roentgen rays.

DISCUSSION

The data so far described indicate that the growth inhibiting effect of ionizing radiation can be increased by elevated temperatures. Practical application of this technique depends on the knowledge of optimal conditions of combination. There exists suggestive evidence that simultaneous application or immediate subsequence are the methods of choice. It is unknown, however, which particular temperature range is optimal. The effect of ionizing radiation depends upon many factors, *i.e.*, oxygen tension, mitotic activity, metabolic rate, and water content.[31,41] All of these factors are temperature dependent and their maximum change occurs in different temperature ranges.[29]

At elevated temperatures the following effects have been observed (Fig. 2): Temperature increases of 0.5°C. or even less cause considerable active hyperemia. At slight temperature increases this hyperemia is mainly due to thermoregulatory mechanisms and serves the equalization of temperature by convection. Up to 5°C. above normal temperature, the blood supply exceeds the actual metabolic demand and leads together with thermoregulatory hyperventilation to increased oxygen tension and alkalosis in the tissues. At temperatures of 2–3°C. above normal, the mitotic rate may increase 100 per cent or more. At higher temperatures mitosis is at first arrested in metaphase, then inhibited. In man, the metabolic rate is increased

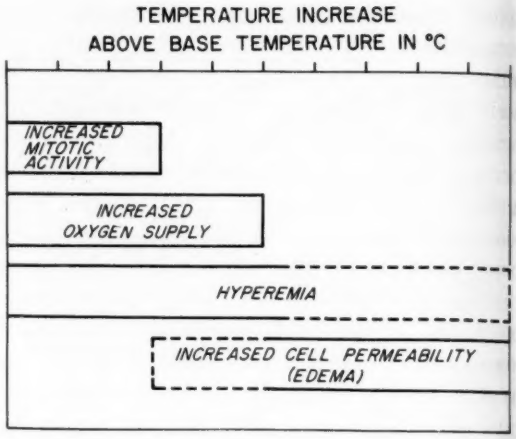

FIG. 2. Influence of heat on tissues.

by 15 to 20 per cent per degree of centigrade of increasing body temperature. A critical point is reached when the metabolic demand exceeds the supply. This point is different for various tissues and various individuals, depending on the local metabolic demand as compared with vascularization and cardiac output. Further temperature increases may cause peripheral vascular collapse, cardiac decompensation and other untoward side effects. Up to this point the results of combined treatment would be due to enhanced normal cell function stimulated by elevated temperatures. Potentially, however, cell impairment by highly elevated temperatures could also be useful at least for local treatment. At temperatures of 7 or more degrees centigrade above normal, the water content of tissues increases excessively due to edema caused by vascular heat injury. Thus, the optimal temperature for combination with roentgen rays is expected to be in the range of 0.5 to 4°C. above normal levels. Further basic research will be necessary in order to appreciate and to differentiate the various factors involved.

Studies concerning the optimal temperature for the maximum complementary effect have not been reported. Likewise, studies concerning the optimal time sequence so far have been incomplete. Most authors used only one sequence, and the few papers with comparative results are

somewhat contradictory concerning immediate sequences. Over long time intervals, irradiation followed by hyperthermia seemed to be most effective, the effectiveness decreasing with the increase of time between the two treatments. This might be anticipated because the latent effect of ionizing rays lasts longer than that of hyperthermia. It seems plausible, therefore, that simultaneous application should be most effective, roentgen irraditaion followed by heat therapy less effective, and hyperthermia followed by roentgen irradiation least effective. Whether or not this hypothesis is valid is to be examined in future experiments.

Since the treatment of cancer relies on the differential sensitivity of normal and cancerous tissue to the therapeutic agent, it must be ascertained whether this differential sensitivity is altered by elevated temperatures. No report concerning this problem was found in the literature.

Finally, the results so far published on untoward side effects are insufficient. This holds true especially for skin damage and possibly for the increase of metastatic rate.

The combination of irradiation with elevated temperatures is potentially a promising method. Further research, however, will be necessary to evaluate the optimal conditions and the possible untoward side effects.

SUMMARY

A review of the literature suggests that ionizing radiation is more damaging to cancer cells at elevated temperatures. The combination of heat and roentgen ray therapy is therefore potentially useful against "radioresistant" and poorly accessible tumors. Further critical studies are necessary in order to elucidate the nature of the synergism involved, to determine the optimal sequence, and to investigate unfavorable side effects on the host.

Oleg Selawry, M.D.
Roswell Park Memorial Institute
666 Elm Street
Buffalo 3, New York

REFERENCES

1. ALLEN, F. M. Biological modification of effects of roentgen rays. II. High temperature and related factors. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1955, *73*, 836–848.
2. ARONS, I., and SOKOLOFF, B. Combined roentgenotherapy and ultra short waves. *Am. J. Surg.*, 1937, *36*, 533–543.
3. BARTH, G. In: Lampert-Selawry, Körpereigene Abwehr und bösartige Geschwülste. Haug Verlag, Ulm/Donau, 1957, p. 117.
4. BARTH, G. Neue Gesichtspunkte zur Kombination von Röntgentherapie, Chirurgie und Pharmakologie bei malignen Tumoren. Oct. Congr. Internation. Radiol., Book of Abstracts, Mexico City, Mexico, 1956, 172.
5. BAUMEYER, S. Über die Wirkung der Kurzwellenbehandlung auf maligne Tumoren. *Strahlentherapie*, 1938, *62*, 373–375.
6. BERING, F., and MEYER, H. Experimentelle Untersuchungen über die Sensibilisierung von Röntgenstrahlen mittels Wärmedurchstrahlung. *München. med. Wchnschr.*, 1911, *58*, 1000–1002.
7. BERKMAN, T., and DESSAUER, F. Versuche die fraktionierte Bestrahlung durch Provokation sensibler Zellphasen zu unterstützen. *Strahlentherapie*, 1937, *58*, 551–556.
8. BIRKNER, R., and WACHSMANN, F. Über die Kombination von Röntgenstrahlen und Kurzwellen. *Strahlentherapie*, 1949, *79*, 93–102.
9. CHRISTOPHERSEN, J., PRECHT, H., and HENSEL, H. Temperatur und Leben. Springer-Verlag, Berlin, 1955.
10. CRAMER, H. Vorbehandlung, Behandlung und Nachbehandlung von Tumoren, speziell Mammatumoren. *Med. Ztschr.*, 1944, *1*, 83–85.
11. CRAMER, H. Problematik der Geschwulstkrankheiten in der Jetztzeit. *Med. Klin.*, 1946, *41*, 337–341.
12. DALICHO, W. A. Erfahrungen mit Überwärmungen maligner Tumoren in Kombination mit der Strahlentherapie. In: Lampert-Selawry, Körpereigene Abwehr und bösartige Geschwülste. Haug Verlag, Ulm/Donau, 1957, pp. 109–115.
13. DELARIO, A. J. Methods of enhancing roentgen ray action. *Radiology*, 1935, *25*, 617–627.
14. DENIER, A. Essai de traitement de tumeurs inoperables. Leur radiosensibilisation par les micro-ondes de 80 cm. associées au surdosage roentgenothérapique rendu possible par les ondes infrarouges. *Arch. d'électric. méd.*, 1936, *44*, 403–410.
15. DENIER, A. Les ondes hertziennes ultra courtes de 80 cm. *J. de radiol. et d'électrol.*, 1936, *20*, 193–197.
16. DOUB, H. Osteogenic sarcoma of clavicle treated

with radiation and fever therapy. *Radiology*, 1935, *25*, 355–356.

17. ENGEL, J. P., HERRICK, J. F., WAKIM, K. G., and KRUSEN, F. H. Effect of microwaves on bone marrow and on adjacent tissues. *Arch. Phys. Med.*, 1950, *31*, 453–461.
18. FRY, W. J., and FRY, R. B. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes-experiment. *J. Acoust. Soc. A.*, 1954, *26*, 311–317.
19. FRY, W. J., MOSBERG, W. H., JR., BARNARD, J. W., and FRY, F. J. Production of focal destructive lesions in central nervous system with ultrasound. *J. Neurosurg.*, 1954, *11*, 471–478.
20. FUCHS, G. Zur Sensibilisierung strahlenrefractärer Carcinome durch Kurzwellen. *Klin. Wchnschr.*, 1935, *14*, 1582.
21. FUCHS, G. Über die Sensibilisierung röntgenrefractärer Neoplasmen durch Kurzwellen. *Strahlentherapie*, 1936, *55*, 473–480.
22. FUCHS, G. Die kombinierte Kurzwellen-Röntgentherapie maligner Tumoren. *Wien. med. Wchnschr.*, 1952, *102*, 583–585.
23. FUCHS, G. Zur Sensibilisierung maligner Tumoren durch Ultra-Kurzwellen. *Strahlentherapie*, 1952, *88*, 647–653.
24. FUCHS, G. Versuche zur Steigerung der Strahlensensibilität maligner Tumoren. *Radiol. Austriaca*, 1952, *5*, 117–126.
25. GRUNER, R. Vorversuche zur Hyperthermiebehandlung des Oesophaguscarcinoms. *D. Heilkunst*, 1951, *64*, 133–137.
26. HALL, B. V. Clarification of differences in radiosensitivity of tumors irradiated in vitro and in vivo on basis of effect of oxygen on radiosensitivity. *Cancer Res.*, 1952, *12*, 268.
27. HARTL, J. Überwärmungsbehandlung von Krebskranken. In: Lampert-Selawry, Körpereigene Abwehr und bösartige-Geschwülste. Haug Verlag, Ulm/Donau, 1957, pp. 115–116.
28. HEEREN, J. G. Röntgen-Bestrahlung in Kombination mit Ultra-Kurzwellen und Insulin-Injectionen. *Strahlentherapie*, 1940, *68*, 444–459.
29. HEILBRUNN, L. V. An Outline of General Physiology. Third edition. W. B. Saunders Company, Philadelphia and London, 1952.
30. HILL, L. Actions of ultra short waves on tumors. *Brit. M. J.*, 1934, *2*, 370–371.
31. HOLLAENDER, A. Radiation-Biology. Vol. I. McGraw Hill Book Company, Inc., New York, 1954.
32. IREDELL, C. E. Two cases illustrating action of short wave diathermy in producing sensibilization to action of radium. Internat. Kurzwellen Kongr. M. Perles, Wien, 1937, 324–328.
33. JARES, J. J., and WARREN, S. L. Combined effects of roentgen radiation and fever upon malignant tumors. *Cancer Problem Sympos.*, 1937, 225–226.
34. JUUL, J. Dosage, duration of treatment and reactions in protracted-fractional roentgen treatment with special reference to carcinoma of upper air passages. *Acta radiol.*, 1938, *19*, 433–442.
35. JUUL, J., and KEMP, T. Über den Einfluss von Radium- und Röntgenstrahlen, ultravioletten Licht und Hitze auf die Zellteilung bei warmblütigen Tieren; Studien an Gewebekulturen. *Strahlentherapie*, 1933, *48*, 457–499.
36. KOLLE, W., LAUBENHEIMER, K., and VOLLMER, H. Wie ist die Schädigung von Zellen in Gewebe-Kulturen die mit menschlicher und tierischer Haut in Kontakt gebracht werden, zu erklären? *Med. Klin.*, 1933, *29*, 417–420.
37. KORB, H. Erhöhung der Wirkung von Röntgenstrahlen durch lokale Kurzwellhyperthermie. *Strahlentherapie*, 1939, *65*, 649–656.
38. KORB, H. Über eine Kombination der Röntgenbestrahlung mit der Kurzwellenbehandlung. *Strahlentherapie*, 1948, *77*, 301–303.
39. LAMPERT, H., and Selawry, O. Körpereigene Abwehr und bösartige Geschwülste. Haug Verlag, Ulm/Donau, 1957.
40. LANGENDORFF, H. M. Untersuchungen über die Ultrakurzwellenwirkung auf Impftumoren. *Strahlentherapie*, 1939, *64*, 512–519.
41. LEA, D. E. Actions of Radiations on Living Cells. Cambridge University Press, London, 1955.
42. LEPPER, E. H. Experiments to determine whether variations in temperature influence effects produced when malignant cells are irradiated by radium bromide. *Arch. Middlesex Hosp.*, 1914–1915, *33*, 77–84.
43. MIKAWA, M. Effect of heat and ultra short wave rays on radiosensitivity. I and II. *Jap. J. Obst. & Gynec.*, 1937, *20*, 515–524.
44. MÜHLENHARDT, R. Diss. Kiel., 1938.
45. MÜLLER, C. Eine neue Behandlungsmethode bösartiger Geschwülste. *München. med. Wchnschr.*, 1910, *57*, 1490–1493.
46. MÜLLER, C. Therapeutische Erfahrungen an 100 Kombinationen von Röntgen und Hochfrequenz resp. Diathermiebehandlungen bösartiger Neubildungen. *München. med. Wchnschr.*, 1912, *59*, 1546–1549.
47. NAKAMURA, H., YAMADA, M., TAKANAKA, K., WAKABAYASHI, M., and SASADA, S. Experimental study on checking influence of short and ultra short waves on development and enlargement of malignant tumors. *Gann.*, 1936, *30*, 548–560.
48. OVERGAARD, K. Experimentelle undersoegelser over muligheden af en varmeterapi af maligne tumorer. *Ugesk. f. laeger.*, 1935, *97*, 333–337.
49. OVERGAARD, K. Heat treatment of malignant

tumors. Oct. Congr. Internation. Radiol., Book of Abstracts, Mexico City, Mexico, 1956, 249.

50. Overgaard, K., and Okkels, H. Tierexperimente zur Wärmebehandlung bösartiger Geschwülste. *Ztschr. f. Krebsforsch.*, 1941, *51*, 367–368.

51. Portis, B. Effect of short wave length roentgen rays and diathermy on transplantable rat carcinoma. *Trans. Chicago Path. Soc.*, 1927, *12*, 15–22.

52. Rae, J. W., Herrick, J. F., Wakim, K. G., and Krusen, F. H. Comparative study of temperatures produced by microwave and short wave diathermy. *Arch. Phys. Med.*, 1949, *30*, 199–211.

53. Riviere, C. Radium. Un. Min. Hautkatanga, Brussels.

54. Rohdenburg, G. L., and Bullock, F. D. Influence of heat and radium upon induced immunity against transplanted animal tumors. *J. Cancer Res.*, 1918, *3*, 181–191.

55. Rohdenburg, G. L., and Prime, F. Effect of combined radiation and heat on neoplasms. *Arch. Surg.*, 1921, *2*, 116–129.

56. Sarasin. Haut- und Schleimhautreaktionen bei protrahiertfraktionierter Röntgenbehandlung. *Strahlentherapie*, 1935, *52*, 61–73.

57. Schliephake, E. Spezifische Wirkungen des Ultrakurzwellenfeldes. *Strahlentherapie*, 1936, *57*, 151–164.

58. Schliephake, W. Kurzwellentherapie. Piscator, Stuttgart, 1950.

59. Schmidt, H. E. Zur Röntgenbehandlung tiefgelegener Tumoren. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1909, *14*, 134–136.

60. Schneider, G. H. Ultraschall und Röntgentherapie. *Arch. Phys. Therapy*, 1952, *4*, 411–413.

61. Schwan, H. P., Cartensen, E. L., and Li, K. Electric and ultrasonic deep-heating diathermy. *Electronics*, 1954.

62. Schwarz, G. Über Desensibilisierung gegen Röntgen- und Radiumstrahlen. *München. med. Wchnschr.*, 1909, *56*, 1217–1218.

63. Schwarz, G. Über Partialprozesse der Röntgenreaktion in ihren Beziehungen zum Desensibilisierungs- und Sensibilisierungsproblem. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1933, *47*, 448–454.

64. Scott, L. D. Summary of results of combined fever and x-ray therapy in treatment of hopeless malignancies. *J. Nat. M. A.*, 1944, *36*, 184–186.

65. Selawry, O. Influence of elevated temperatures on growth and morphology of HeLa cultures. *Anat. Rec.*, 1956, *124*, 2–22.

66. Selawry, O. Effect of elevated temperatures on human cell strains of malignant origin. *Cancer Res.*, 1957, *17*, 785–791.

67. Shoulders, H. S., Turner, E. L., Scott, L. D., and Quinn, W. P. Preliminary report on effect of combined fever and deep x-ray therapy in treatment of far advanced malignant cases. *J. Tennessee M. A.*, 1941, *34*, 9–15.

68. Shoulders, H. S., Turner, E. L., and Scott, L. D. Observations on results of combined fever and x-ray therapy in treatment of malignancy. *Southern M. J.*, 1942, *35*, 966–970.

69. Shoulders, H., Turner, E. L., Scott, L. D., and Grant, W. Effect of combined fever and x-ray therapy on far advanced malignant growths. *Radiology*, 1942, *38*, 184–193.

70. Sugiura, K. Effect of high and low body temperatures upon growth of irradiated mouse sarcoma 180. *Radiology*, 1941, *37*, 85–93.

71. Taylor, H. J. Effect of ultra high frequency currents combined with non-lethal doses of radium radiations upon experimental rat tumors. *Brit. J. Radiol.*, 1936, *9*, 467–480.

72. Theilhaber, A. Die Entstehung und Behandlung der Karzinome. S. Karger, Berlin, 1914.

73. Vallebona, A. Strahlensensibilisierung durch physikalische Massnahmen. *Strahlentherapie*, 1939, *65*, 361–368.

74. Warren, S. L. Preliminary study of effect of artificial fever upon hopeless tumor cases. Am. J. Roentgenol. & Rad. Therapy, 1935, *33*, 76–87.

75. Wittenbach, F. Die Bestrahlungsmethoden der Erlanger Frauenklinik bei der Röntgentherapie der weiblichen Genitalkarzinome. *Strahlentherapie*, 1934, *50*, 399–427.

76. Woeber, K. Studium der Wirkung von Hyperthermie durch Überwärmungsbad, Ultrakurzwellen und Ultraschall auf Krebsgewebe sowie biologische Grundlagen einer kombinierten Röntgen-Ultraschall-Behandlung oberflächlicher Tumoren. *Strahlentherapie*, 1954, *95*, 333–366.

77. Woeber, K. Kombinierte Röntgen- und Ultraschallbehandlung beim experimentellen Tierkrebs. *Arch. Derm. Syph.*, 1955, *200*, 349–354.

78. Woeber, K. Die Bedeutung des Ultraschalls für die Dermatologie und seine Anwendung bei Hauttumoren in Kombination mit Röntgenstrahlen. *Strahlentherapie*, 1955, *98*, 169–185.

79. Woeber, K. Combined x-ray ultrasound treatment for dermatological conditions. *Am. J. Phys. Med.*, 1955, *34*, 376–378.

80. Woeber, K. Über Anwendung der Röntgenstrahlen in Kombination mit anderen Behandlungmethoden bei Hauttumoren. In: Lampert-Selawry, Körpereigene Abwehr und bösartige Geschwülste. Haug Verlag, Ulm/Donau, 1957, 127–129.

81. Wood, F. C. Cancer biology and radiation. *Radiology*, 1928, *11*, 388–392.

LOCALIZED ROENTGEN-RAY BEAM IRRADIATION OF THE HYPOPHYSOHYPOTHALAMIC REGION OF GUINEA PIGS WITH A 2 MILLION VOLT VAN DE GRAAFF GENERATOR*

By H. POURQUIER, M.D.,† J. R. BAKER, A.I.M.L.T., F.R.M.S.,‡
G. GIAUX, M.D.,§ *and* K. BENIRSCHKE, M.D.‖
BOSTON, MASSACHUSETTS

THE purpose of this study was the determination of the radiosensitivity of the pituitary gland and the hypothalamus. The application of large doses of roentgen rays to this specific area without damage to the remaining brain tissues or systemic radiation reaction has been one of the main difficulties encountered. In order to avoid such an undesirable effect, a small beam of roentgen rays was directed accurately to this area, a process that is most easily accomplished by a localized beam of small cross-section.

The pituitary gland of adult animals is not a very radiosensitive organ, while the hypothalamus and brain stem are relatively easily damaged by irradiation. Therefore, previous workers have intentionally avoided irradiation of the hypothalamus in their studies of irradiation effects on pituitary[1,8,20,24] or brain tissues.[2,9,23]

We employed the following method in this study to ascertain the changes occurring after irradiation of these specific structures and to compare their radiosensitivity to that of other areas of the brain. A series of previous reports[10,11,24] indicates that single doses from 2,000 to 3,000 r directed to the pituitary gland of different mammals were without histologic sequelae or recognizable persistent physiologic consequences. Doses of 5,000 or more roentgens are followed by pyknosis of the anterior lobe cells. However, the physiologic changes produced by such doses have not yet been fully evaluated. In toads, the application of 20,000 r does not result in a decrease of thyrotrophin during a three weeks' study.[1] In humans,[17] dosages up to 10,000 r given over a two months' period did not cause histologic changes in the pituitary gland in one year.

Tobias *et al.*[30] used rats and found that only very high doses of roentgen rays (18,900 rep) were able to destroy the pituitary rapidly; with lower doses (6,300 rep), destruction was not complete for nine months.

As for the hypothalamus, because of the presence of vital centers in this area and of their relative radiosensitivity, it is easy to detect the anatomic lesions that precede those of other parts of the brain.

Other authors have made it clear that a delayed response can be observed after irradiation of the nervous tissue which is peculiarly evident in the white matter. In our experiment we have attempted to study especially the time of development of the delayed brain necrosis according to the dose given; we have also attempted to determine whether its principal cause is the result of destruction of brain tissue or vascular damage.

MATERIAL AND METHODS

This study was performed on 70 adult but not fully grown guinea pigs, mostly male, weighing between 700 and 900 gm.

To insure exact localization of the center

* This work was done while Dr. Pourquier was a Research Fellow of the Medical Research Foundation of Boston, at the Cancer Research and Cancer Control Unit of Tufts University School of Medicine. It was supported in part by funds from an institutional grant of the American Cancer Society, New York.

† Present address: Centre Curie, Hôpital Saint-Eloi, Montpellier, France.
‡ Cancer Research Unit and Cancer Control Unit of Tufts University School of Medicine.
§ This work was done while Dr. Giaux was a research fellow in the High Voltage Research Laboratory, Massachusetts Institute of Technology. He is now at the Centre regional anticancéreux de Lille, France.
‖ Associate in Pathology, Harvard Medical School, Boston, Massachusetts.

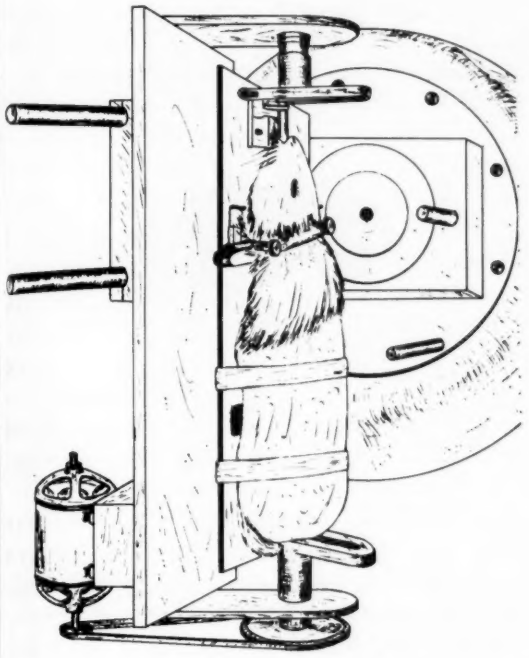

Fig. 1. Apparatus fixing a guinea pig by the external auditory canals and the mandible, allowing a rotational or transverse irradiation.

of the beam of roentgen rays, the heads of the animals were fixed by an apparatus similar to that described by Horsley and Clarke. Two pointed metal rods were inserted in the external auditory canals, and mandible and maxilla were fixed by a clamp. Rods and clamp were fixed to a sheet of metal with a rectangular aperture 2 cm. in width at the level of the irradiated area. This sheet of metal could be rotated in the longitudinal axis of the animal. The animal was placed in the apparatus in order to insure a symmetric and stationary position during the entire procedure (Fig. 1). Previously, it was anesthetized by an intraperitoneal injection of nembutal in order to insure a relaxation of one hour's duration. A standard lateral roentgenogram was then made at 80 cm. after the application of a small piece of lead to the skin in an area corresponding approximately to the projection of the sella turcica. This preliminary roentgenogram indicated the correction to be made for the application of the beam. After correction, a second roentgenogram was made with the 2 million volt Van de Graaff machine. When the exact direction of the beam was thus ascertained, irradiation was begun.

Two types of beam and technique were employed: (1) a 0.5 cm. diameter beam using a collimator of lead 14 cm. thick; and (2) a 1 cm. square beam (at the midline of the head) with a similar collimator 5 cm. thick.

The animals were placed in the beam of a 2 million volt constant potential roentgen-ray generator; the half-value layer in lead measured in a 10×10 cm. field was 7.2 mm. of lead (effective energy beam being above 1.1 mev.). Using the 1 cm. square beam, a transverse irradiation was effected; the target skin distance was 60 cm. A rotational technique was used with the small 0.5 cm. diameter beam. This apparatus was made available by the High Voltage Research Laboratory of the Massachusetts Institute of Technology. Roentgen rays produced at 2 million volts are absorbed almost entirely by the Compton process. A Compton electron and the associated scattered photon are projected in a nearly forward direction, and the side scatter beyond the limit of the primary beam is negligible so that field definition can be maintained at even greater depths of tissue. Therefore, small cross-section beams are more easily obtained than with conventional machines. However, it is not possible to measure the beam intensity with a Victoreen chamber with this method, owing to the cross-section of the beam. Therefore, a photometric technique was employed.

With the Van de Graaff machine, the integrating panel dosimeter is used as monitor and gives an air equilibrium dose at 122.2 cm. in a 10×10 cm. field; correction is made for the distance of irradiation.

The films (Dupont-Adlux) used for the calibration were placed at the same distance from the machine as the animals, surrounded by masonite pressdwood simulating the thickness of the animal's head.

Several different measurements were made: first, with large fields of 5×5 cm.,

using the Victoreen chamber to determine the dose at the film; and then the small field was used, utilizing different time exposures. All the films originating from the same batch were developed simultaneously with equal agitation. In all experiments the Victoreen chambers were used under equilibrium conditions. The beam was homogeneous over the entire area and, at a distance of about 0.5 mm. from the edge, the intensity was reduced by only 5 per cent. For the lateral single port, the entrance and the exit doses referred to the center of the brain were respectively 105 and 95 per cent. These values apply for an average brain width of 2 cm.

The tissue dose at the midline of the brain was determined within an accuracy of ± 5 per cent, by employing this method. With both types of collimator the measured output of the machine was 75 per cent ± 2 per cent of those values determined by the inverse square law in the case of the 5×5 cm. square field. Inasmuch as rotation irradiation was used as well as lateral transverse irradiation, the isodose distribution had to be determined for a plan perpendicular to the axis of rotation. A small field was placed in a lucite cylinder 4 cm. in diameter and rotated around the central axis. The dosage distribution in this cylinder was determined by photographic means similar to those previously described. The dose at the surface of a 0.5 cm. sphere was found to be 75 per cent of the dose at the center. At a distance of 1 cm. from the axis the brain dose decreased to 15 per cent of the axis dose (Fig. 2).

Of the 70 animals studied, 35 received transverse irradiation and 35 rotational irradiation. In each of these two groups, 6 animals were given the following tissue dosage: 2,700, 3,000, 4,500, 7,500, 18,000 r at one application. Some intermediate dosages were also administered (11,000 and 15,000 r).

The rate of irradiation varied between 160 and 350 r per minute. The animals were then returned to their cages together with control animals and fed on a standard

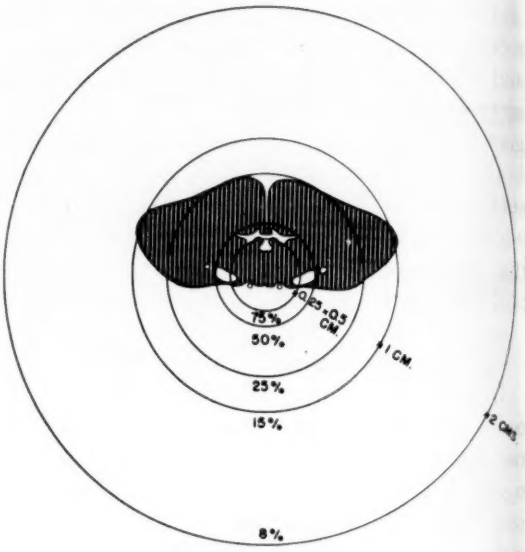

FIG. 2. Radiation distribution for rotational irradiation (0.5 cm. diameter field; studies made in a lucite phantom).

diet. They were weighed every week and some were studied in metabolic cages to ascertain water balance. One animal of each group was killed within two weeks after roentgen-ray application and others among those receiving low doses of irradiation were killed at varying periods within two to three months. Still others of each group were sacrificed at the onset of weight loss. The remaining animals were autopsied immediately after death or sacrificed and autopsied when death seemed imminent. Animals in the group receiving 2,000 and 3,000 r increased in weight steadily and were sacrificed after six months of apparent good health.

Exsanguination was performed under light ether anesthesia. Brain and endocrine organs were weighed and fixed in 8 per cent formol-saline prepared from USP formaldehyde. The pituitary glands were fixed in formol-sublimate diluted with an equal volume of 8 per cent formol-saline and fixed for six hours and dehydrated without prior washing in water, embedded in paraffin and serially sectioned at four microns for the purpose of accurate cell counts. They were stained by the Tripas method of Pearse[26]

and also by the chrome alum hematoxylin method (Gomori).[12] Routine hematoxylin and eosin stains were used for the paraffin sections of the following tissues: pituitary gland, adrenal cortex, testis, thyroid and brain. Brain sections were taken by coronal section through the hypothalamus. The adrenal glands were also sectioned by freezing technique and stained with sudan IV and hematoxylin.

RESULTS

Contrary to our expectations, no deaths occurred earlier than three weeks after irradiation. All animals recovered without signs of radiation sickness, even those receiving the highest dosage. They had to be exposed to doses exceeding 15,000 r to show initial cessation of growth as measured by weight. When a dosage between 7,500 and 12,000 r was given, there was an initial reduction of growth which, however, resumed after two weeks. There was no immediate effect on normal growth at dosages below 7,500 r.

The occurrence of degenerative changes in the hypothalamus, as evidenced by microscopic examination, caused increased weight loss and lack of food intake with eventual death. In addition to these symptoms, many of the animals appeared to be blind and some exhibited signs of equilibrium disturbance. During the course of this study it was discovered that animals examined at the onset of weight loss or occurrence of vegetative symptoms displayed early signs of hypothalamic lesions that increased in severity with time. Figure 3 demonstrates weight loss and first occurrence of neurologic symptoms plotted against time and intensity of irradiation.

The food intake during the period of weight loss decreased considerably without any significant change in water intake until the last few days of life. Animals irradiated with small beams had a somewhat more delayed course of weight reduction and death than those irradiated with the 1 cm. square beam.

It was also noted that the testis assumed

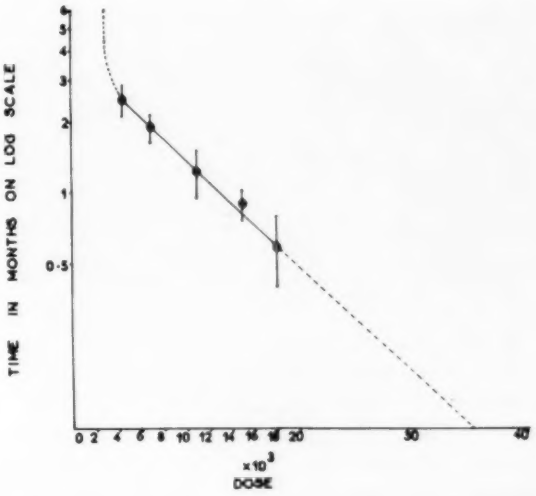

FIG. 3. Doses in roentgens plotted against logarithm of the time. The vertical bars are the standard errors of the mean value. Straight line represents latent time (before neurologic symptoms and brain necrosis) between 4,500 and 18,000 r. Broken line indicates the hypothetical curve.

an intraperitoneal position at the initial period of weight loss. Terminally, the animals appeared severely ill, their skin was dry, and they were apathetic and listless.

MICROSCOPIC FINDINGS

The changes in the brain after transverse and rotational irradiation resembled one another and were located in similar areas within the hypothalamus and adjacent tissues. There was close correlation between findings of the same dosage given in both types of techniques.

Generally, the earliest change microscopically detectable consisted of focal demyelinization in the optic tracts and cerebral peduncles (Fig. 4), as well as "hyaline" degeneration of small vessels and cerebral arteries in the hypothalamus and adjacent structures. It was remarkable to encounter almost complete absence of changes in the cerebral cortex and meningeal vessels even with high dosage irradiation. The only change occasionally encountered in meningeal vessels was swelling of vascular endothelial cells. Simultaneous degeneration of the subependymal area frequently oc-

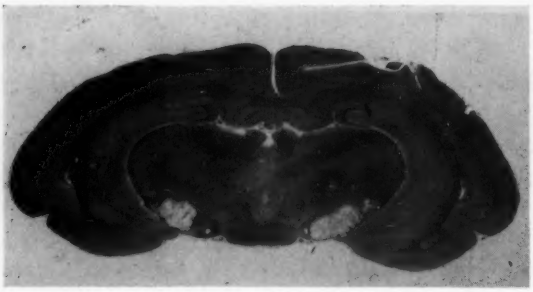

Fig. 4. Bilateral and selective demyelinization of optic tracts and peduncles two months after a dose of 4,500 r given in transverse irradiation. (Weil myelin stain ×3.)

Fig. 5. Extensive demyelinization of optic tracts and cerebral peduncles. (Weil myelin stain ×10.)

curred in animals with optic tract degeneration.

There were no significant pathologic findings when animals were killed immediately prior to the expected weight loss. The onset of weight loss produced a progressive myelin degeneration that was most pronounced at the time of death. Twelve animals received 2,000 or 3,000 r. All were killed after six months of apparent good health, with the exception of one that died at the end of five months with an intraventricular hemorrhage but no brain necrosis. On the whole, the histologic lesions observed in this group were very small and the least significant. In animals receiving 2,000 r, the tissues were almost entirely normal. There were only a few round inflammatory cells around the basilar arteries.

Among the others there was a minimal increase in glial cells and occasional pyknotic cells in the supra-optic nucleus. No necrosis was present. The basilar arteries revealed irregular walls that were slightly hyalinized and vacuolated with edema. There were some bizarre nuclei in their walls. Some small vessels in the brain substance showed similar changes with narrowing of the lumen and perivascular round cell infiltration in the meninges. The ependyma was normal.

Twelve animals received 4,500 r tissue dose, 6 with transverse irradiation, 6 by rotation. They began to lose weight at an average of ten weeks and died at twelve and one-half weeks; 4 animals were sacrificed two, four and seven weeks after irradiation and demonstrated no degenerative changes in the brain. In one animal there was occasional slight thickening of the capillaries in the hypothalamus without degenerative changes in the brain substance.

In addition, chrome alum hematoxylin stains showed no alteration of ganglion cells in the supra-optic nuclei and the secretion of the posterior lobe was average. Conversely, there was extensive demyelinization and necrosis of the optic tracts, cerebral peduncles (Fig. 5) as well as the subependymal regions of the lateral ventricles in animals killed at eight and a half, nine and a half and eleven weeks and in those dying at twelve weeks.

There were areas of degeneration and hemorrhages in the central portion of the hypothalamus that comprised part of the fornix and hypothalamic nuclear structures. These lesions appeared randomly distributed, but usually if the animals were irradiated transversely, they seemed to be more marked on the side of their lateral subependymal degeneration. In the case of rotational irradiation, the lesions were of a central nature (Fig. 6) with degeneration and vascular changes near the third ventricle. The areas of necrosis were grossly vacuolated and revealed no viable cells in their centers while at the periphery there

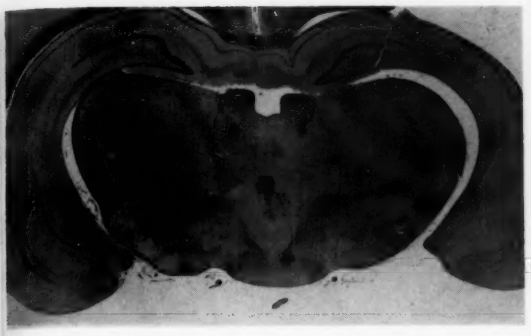

Fig. 6. Section of brain after rotational irradiation with 4,500 r. The severest lesions are in the central diencephalic region with numerous areas of hemorrhage. (Hematoxylin-eosin stain ×6.)

was marked leukocytic infiltration. The vessels in these areas were necrotic and thrombosed. In areas of hemorrhage, which usually occurred adjacent to the third ventricle, there was marked dilatation of small vessels with sludged, hyalinized walls. The vessels frequently assumed a "plexiform" pattern (Fig. 7) and showed incipient thrombosis. The cerebral arteries at the base of the brain had undergone degeneration with segmental destruction of elastic and muscular coats (Fig. 8 and 9). The ependyma was flattened and occasionally absent. No changes were observed in the ganglion cells of the cortex, nor the supraoptic nuclei and paraventricular nuclei. The Gomori positive material in the posterior lobe appeared somewhat decreased in amount.

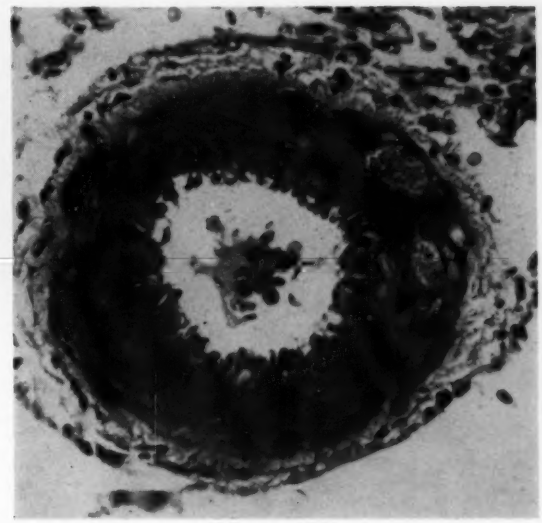

Fig. 8. Early changes in an artery at the base of the brain. Destruction of endothelium and hyaline deposit in media. (Hematoxylin-eosin stain ×150.)

The group of animals receiving 7,500 r began to lose weight at an average of 7.7 weeks and died within ten weeks. Two of those sacrificed before the beginning of weight loss showed only slight vacuolization of the optic tracts, occasionally, an increase of microglial cells and vascular adventitial cells, and swelling of vascular endothelium in the hypothalamus.

With the onset of weight loss, there was a profound destruction of the same areas described in the previous group. Compared to these animals, the changes were more extensive and severe. Frequently, there were

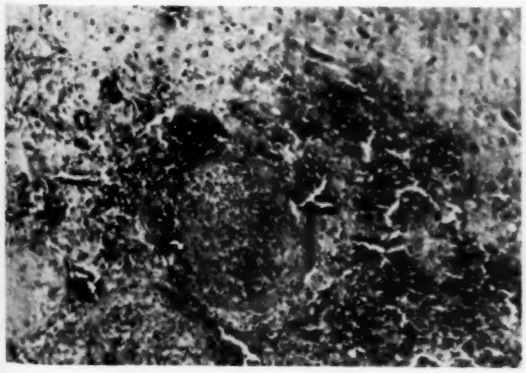

Fig. 7. Dilated vessels and angiomatous appearance of diencephalic region. Areas of hemorrhage and necrosis. (Hematoxylin-eosin stain ×50.)

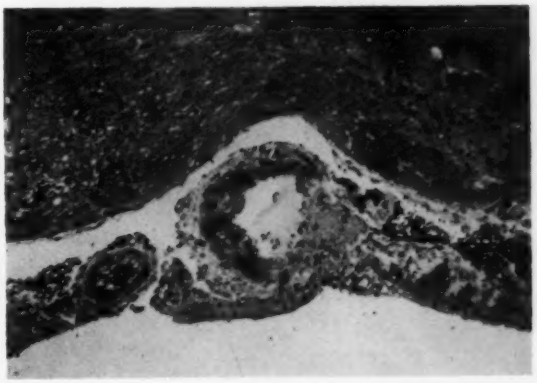

Fig. 9. Segmental destruction of an artery of base of brain with hemorrhage after 4,500 r. (Hematoxylin-eosin stain ×150.)

satellitosis, lymphocytic cuffing of vessels and marked perivascular hemorrhage. Also, occasional hemosiderin deposits were noted in perivascular areas.

Animals receiving 11,000 r began to lose weight at an average of five weeks and died at an average of nine weeks. All those that died or were sacrificed within five weeks or more following irradiation showed degenerative changes in the areas previously described. The selectivity of destruction of the optic tracts, cerebral peduncles and subependymal areas was again noted. In the areas affected and in the immediately adjacent tissues, the vessels revealed a marked hyalinization of the walls, dilatation and transudation of proteinaceous material into the periphery. There were also degeneration of ependymal cells, phagocytosis of necrotic debris, swelling and proliferation of astrocytes. The absence of vascular change in the meningeal vessels was striking. Few animals displayed vacuolization of ganglion cells of the supra-optic nuclei, and there were no changes in the paraventricular nuclei.

Those animals receiving 15,000 r began to exhibit brain necrosis at 3.6 weeks, those receiving 18,000 r, at 2.4 weeks.

Only one of the animals receiving 15,000 and 18,000 r died as early as five days after irradiation. No degenerative changes were found at autopsy and on microscopic examination. However, the presence of an acute meningo-encephalitis and hepatitis led us to believe that death was caused by intercurrent infection rather than the results of irradiation.

The degenerative changes discovered in the other animals of this group were extensive and again affected the optic tracts, cerebral peduncles, hypothalamus and subependymal areas of the lateral ventricles. Recent hemorrhage (Fig. 10) was seen in areas of plexiform dilatation of small vessels of the hypothalamus. There was marked infiltration with polymorphonuclear leukocytes and widespread necrosis of the ependyma. The paraventricular nuclei were preserved. The oligodendroglial cells

FIG. 10. Recent hemorrhage in the hypothalamus and necrosis in optic tract after 15,000 r. (Hematoxylin-eosin stain ×10.)

showed pyknosis and early degeneration. As early as three weeks after irradiation, smaller vessels of the hypothalamus showed extensive hyalinization of the walls, dilatation, thrombosis and marked swelling of endothelial cells. Occasional meningeal vessels showed beginning of hyalinization of the walls. The walls of the few meningeal veins present were infiltrated with inflammatory cells.

Pituitary glands were examined through the courtesy of Dr. Agnes S. Burt. The distribution of the anterior lobe cells was determined by actual cell counts in a number of instances at various intervals after different exposures. The results of the count varied and were not very conclusive. In some instances, the cell counts compared closely with those of nonirradiated, starved animals. There was a tendency toward reduction of acidophils and an inconstant increase in sparsely granulated basophils. A marked nuclear enlargement could be seen in the sparsely granulated basophils.

The only consistent change was that of nuclear pyknosis (Fig. 11), chiefly in the acidophils, coarsening of nuclear pattern and tendency toward clumping. This became more pronounced at higher dosage and after long time intervals between irradiation and death. These changes were not apparent in animals sacrificed a few days after irradiation. The irradiated pitui-

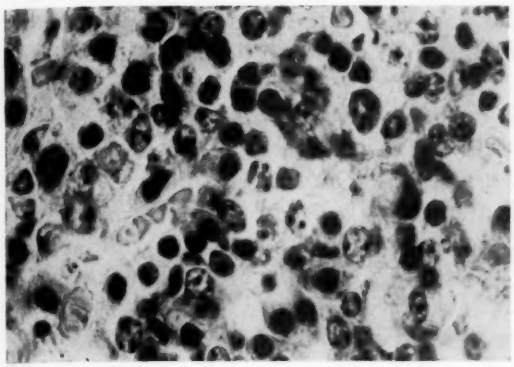

Fig. 11. Anterior pituitary gland two months after rotational irradiation with 4,500 r. The only important change is a nuclear pyknosis of the acidophil cells. (Hematoxylin-eosin stain, oil, ×1,000.)

taries showed a slight decrease of relative and absolute weight compared to those of the control animals, but this is not statistically significant.

DISCUSSION

During the clinical course of the irradiated animals it became evident that none of them suffered from radiation sickness. Their deaths can only be explained by extensive degenerative changes of hypothalamus and adjacent areas found at autopsy. Later in the course, a progressive deterioration of the animals as evidenced by anorexia, loss of weight and neurologic symptoms took place. This is in keeping with the findings of Ross, Leavitt, Holst and Hicks, as quoted by Hicks.[16] These authors noted that the nervous system does not play an important role in the production of the radiation syndrome.

The pathologic findings encountered in the brain were minimal if the animals were sacrificed before the onset of weight loss and occurrence of neurologic symptoms. Once the animals exhibited any of these disturbances, there was invariably more or less extensive degeneration in portions of the irradiated brain. The fact that no brain necrosis was observed after a six month interval and doses of 3,000 r is not astonishing. Indeed, Arnold *et al.*[2] by using the 23 mev. betatron, observed a delayed radionecrosis with doses of 3,000 to 5,000 r after six months or more.

One of the more significant results of this study concerns the relationship between the roentgen-ray dosage and the latent period of brain necrosis. It became evident that a fixed dose of roentgen rays produced brain lesion at a certain time interval after irradiation.

In Figure 3, the logarithms of the latent interval have been plotted against dose; an exponential relationship appears to exist between time and dose, since the points of the curve fall on a straight line between 4,500 and 18,000 r, within the errors of experiment.

A mathematical correlation of this type has already been suggested by Pennybacker *et al.*,[27] and Zeman,[32] but it has not been previously substantiated. According to Figure 3, a dose of about 35,000 r would cause a brain necrosis in a few days. Hen-

Table I

QUANTITATIVE STUDIES

Guinea Pig No.	Rx	Time after Rx	Cells Counted	SGB	NB	Ac	Chr
106	Control	—	2,623	13.2	1.7	50.0	35.1
203	Control	—	3,093	9.6	2.5	52.9	25.1
43	15,000 r	3 weeks	1,828	9.1	2.7	42.3	45.9
21	18,000 r	3 weeks	2,975	14.6	3.7	40.7	41.0
40	18,000 r	4 weeks	1,986	8.2	2.4	33.4	56.0
44	4,500 r	9 weeks	2,073	8.7	1.9	25.4	64.1
108	4,500 r	10 weeks	2,005	23.0	2.0	33.7	41.3

NB = normal basophils; SGB = sparsely granulated basophils; Ac = acidophils; Chr = chromophobes.

shaw[13] has shown that a single massive dose of 50,000 r given within a few hours would produce an immediate cellular damage after total body irradiation.

It is clear that with lower doses this exponential relationship is no longer true. For single doses between 2,000 and 3,000 r the latent time should be placed between six months and two years. Russell, Wilson and Tansley[28] have not observed cerebral damage in dogs at the end of two years after a dose of 2,030 r. With monkeys, however, Arnold *et al.*[4] have seen a delayed brain necrosis eight months after a betatron dose of 1,500 to 3,000 r (23 mev. rays). With even lower doses, the recovery process is predominant, and the destructive lesions may never appear.

However, it is likely that the cerebral radiosensitivity is a biologic quantity that remains relatively constant. It would be interesting to determine for both a single and fractionated dose all the points of the above curve by long-term observations.

This type of delayed radionecrosis of cerebral tissues has been described in a number of papers.[4,7,14,23] Some authors[23,28] have incriminated vascular alterations as the sole cause of this degeneration, while others[3,9] have suggested a specific radiosensitivity of certain structures of the brain.

In the present experiment it was striking to observe that only certain areas of the irradiated portions of the brain were damaged while others remained seemingly unaltered. While this finding has been noted previously, it does not rule out the possibility that apparently normal areas undergo degenerative changes at a later date, as has been demonstrated for less vital parts of the brain.[2]

The regions selectively destroyed in our experiment were the optic tract, cerebral peduncles, subependymal white matter and certain areas in the hypothalamus. While the former lesions do not appear to be secondary to vascular changes, the destructive areas in the hypothalamic gray matter were frequently associated with extensive hemorrhage and vascular degeneration. It was remarkable to see pronounced vascular changes in the hypothalamus and absence of significant degenerative lesions of meningeal vessels. The cortical neuronal elements were not significantly damaged in any of the animals and only rarely were there degenerative changes of the ganglion cells in the supra-optic and paraventricular nuclei. This latter finding was only made in animals irradiated with very high dosage and differs from the observation of Arnold[5] in monkeys.

The effect on the various types of glial elements was in keeping with reports of Hicks[15,16] and others. It appeared to the present observers that the damage to the various areas of the brain is the result of a selective sensitivity of myelin sheaths as well as smaller vessels. From the examination of the transversely irradiated animals, it appeared that the degenerative lesions were confined rigidly to the areas traversed by the beam. The areas of degeneration were strongly delineated in general, and within 50 microns, normal brain tissue was present alongside necrotic areas.

The changes in the pituitary were small when compared with those of the brain. In none of the animals was there any evidence of vascular degeneration and there was no necrosis. Irradiation with more than 4,500 r resulted in a random pyknosis of cells, and a change in cellular distribution. This consisted chiefly in a reduction of the acidophils and an inconstant increase of sparsely granulated basophils. The nuclear pyknosis and decrease in acidophils may be suggestive of decreased secretory activity. On the other hand, the greater number of basophils could be interpreted as an increased need for adrenal cortical hormones. The inconsistency of results concerning the cellular distribution of the pituitary gland after irradiation in previous reports is discussed at length in a paper by Mateyko and Charipper.[24] However, it appears from the present study that these quantitative changes of the anterior lobe were not reflected in a significant alteration of its functional capac-

ity. Examination of the testes and adrenal glands in our experiment revealed no appreciable changes in weight or histologic structures during the symptom-free interval. With onset of weight loss, etc., there was a uniform testicular weight loss which was generally proportional to that seen in starved animals. On the other hand, this atrophy of the testes need not be specific but may be the result of a hypothalamic lesion as indicated by reports of McCann[25] and others.

Conversely, the absolute weight of the adrenal glands increased markedly. Histologically, this was a reflection of an increase in thickness of the cortex and intense sudanophilia of the inner portion of the fasciculate layer with disappearance of lipid material in the zona glomerulosa.

SUMMARY

Small cross-sections of beams were easily obtained with a 2 million volt roentgen ray generator, permitting localized irradiation of the hypophysohypothalamic region of adult guinea pigs. Dosage was determined by roentgenographic means. High doses from 2,000 to 18,000 r were given in a single application. No radiation sickness was noted.

After a symptom-free interval, which varied exponentially with the intensity of the irradiation between 4,500 and 18,000 r, there was selective degeneration occurring focally mostly in the white matter of the brain. This alteration involved the optic tract, cerebral peduncles, areas of hypothalamus and the subependymal area of the lateral ventricles. It appeared to be independent of simultaneously occurring vascular changes.

There was no appreciable effect on the cortex, neurons and meningeal vessels. Even with doses above 4,500 r, the pituitary gland showed no necrosis or vascular changes. The general picture demonstrated reduction of acidophils and an increase of sparsely granulated basophils. Random pyknosis was more marked at higher dosage and there was a change in the time interval between irradiation and death of the animal. The examination of other endocrine glands suggested continuing stimulation by the pituitary gland after irradiation.

It was impossible to decide from these experiments whether the pituitary gland was so severely damaged as to undergo necrosis in the future since the adjacent cerebral structures were damaged more readily, thus preventing survival of the irradiated animals.

Kurt Benirschke, M.D.
Boston Lying-in Hospital
221 Longwood Avenue
Boston 15, Massachusetts

We wish to thank Dr. Freddy Homburger, Tufts University School of Medicine and Dr. J. G. Trump, Director of the High Voltage Research Laboratory of the Massachusetts Institute of Technology for placing the facilities of their departments at our disposal and for their advice and encouragement. We are also indebted to Dr. A. Burt for her invaluable assistance in examining the slides of the pituitary glands, to Dr. S. P. Hicks for his generous and authoritative advice and to R. C. Granke of the High Voltage Laboratory for his cooperation in the 2 mev. roentgen-ray dose calibration and positioning techniques.

REFERENCES

1. Allen, B. M., Schjeide, O. A., Piccirillo, R. T., and Kowitz, G. Capacity of anterior pituitary gland to function after heavy irradiation. *J. Exper. Zool.*, 1953, *124*, 131–145.
2. Arnold, A., Bailey, P., Harvey, R. A., Haas, L. L., and Laughlin, J. S. Changes in central nervous system following irradiation with 23-mev. x-rays from betatron. *Radiology*, 1954, *62*, 37–46.
3. Arnold, A., Bailey, P., and Harvey, R. A. Intolerance of primate brainstem and hypothalamus to conventional and high energy radiations. *Neurology*, 1954, *4*, 575–585.
4. Arnold, A., Bailey, P., and Laughlin, J. S. Effects of betatron radiations on brain of primates. *Neurology*, 1954, *4*, 165–178.
5. Arnold, A. Effects of x irradiation on hypothalamus: possible explanation for therapeutic benefits following x-irradiation of hypophysial region for pituitary dysfunction. *J. Clin. Endocrinol.*, 1954, *14*, 859–868.
6. Beierwaltes, W. H. X-ray treatment of malig-

nant exophthalmos; report of 28 patients. *J. Clin. Endocrinol.*, 1953, *13*, 1090–1100.

7. BODEN, G. Radiation myelitis of brain-stem. *J. Fac. Radiologists*, 1950, *2*, 79–94.
8. BOND, V. P., SWIFT, M. N., TAKETA, S. T., WELCH, G. P., and TOBIAS, C. A. Indirect effects of localized deuteron irradiation of rat. *Am. J. Physiol.*, 1953, *174*, 259–263.
9. DAVIDOFF, L. M., DYKE, C. G., ELSBERG, C. A., and TARLOV, I. M. Effect of radiation applied directly to brain and spinal cord. I. Experimental investigations on Macacus rhesus monkeys. *Radiology*, 1938, *31*, 451–463.
10. DENNISTON, R. H., II. Influence of roentgen-ray treatments of hypophysis on reproductive systems of ground squirrel and rat. *J. Exper. Zool.*, 1942, *91*, 237–263.
11. FEHR, A. Experimentelle Röntgenbestrahlung der Hypophyse bei Kaninchen. *Schweiz. med. Wchnschr.*, 1936, *66*, 289–291.
12. GOMORI, G. Observations with differential stains on human islets of Langerhans. *Am. J. Path.*, 1941, *17*, 395–406.
13. HENSHAW, P. S. Experimental roentgen injury. III. Tissue and cellular changes brought about with single massive doses of radiation. *J. Nat. Cancer Inst.*, 1943, *4*, 503–512.
14. HICKS, S. P., and WARREN, S. Introduction to Neuropathology. Effects of radiation on nervous system. McGraw-Hill Book Company, Inc., New York, 1950.
15. HICKS, S. P., and MONTGOMERY, P. O. B. Effects of acute radiation on adult mammalian central nervous system. *Proc. Soc. Exper. Biol. & Med.*, 1952, *80*, 15–18.
16. HICKS, S. P. Effects of Ionizing Radiation on the Adult and Embryonic Nervous System. Metabolic and Toxic Diseases of the Nervous System. Vol. XXXII. Williams & Wilkins Co., Baltimore, 1953, pp. 439–462.
17. KELLY, K. H., FELSTED, E. T., BROWN, R. F., ORTEGA, P., BIERMAN, H. R., LOW-BEER, B. V. A., and SHIMKIN, M. B. Irradiation of normal human hypophysis in malignancy: Report of three cases receiving 8,100–10,000 r tissue dose to pituitary gland. *J. Nat. Cancer Inst.*, 1951, *11*, 967–983.
18. KERR, H. D. Irradiation of pituitary tumors; results in fifty cases. AM. J. ROENTGENOL. & RAD. THERAPY, 1948, *60*, 348–359.
19. KORSON, R., and BOTKIN, A. L. Effects of total body x-irradiation on rat pituitary. *Endocrinology*, 1954, *54*, 225–226.
20. LACASSAGNE, A., and NYKA, W. Procédé de destruction de l'hypophyse du lapin par le radon. *Compt. rend. Soc. de biol.*, 1934, *116*, 581–583.
21. LAWRENCE, J. H., NELSON, W. O., and WILSON, H. Roentgen irradiation of hypophysis. *Radiology*, 1937, *29*, 446–454.
22. LIEBOW, A. A., WARREN, S., and DECOURSEY, E. Pathology of atomic bomb casualties. *Am. J. Path.*, 1949, *25*, 853–1027.
23. LYMAN, R. S., KUPALOV, P. S., and SCHOLZ, W. Effect of roentgen rays on central nervous system. Results of large doses on brains of adult dogs. *Arch. Neurol. & Psychiat.*, 1933, *29*, 57–87.
24. MATEYKO, G. M., and CHARIPPER, H. A. Histological effects upon pars anterior of rat following hypophyseal cathode ray irradiation and whole-body x-irradiation. *J. Morphol.*, 1953, *93*, 533–559.
25. MCCANN, S. M. Effect of hypothalamic lesions on adrenal cortical response to stress in rat. *Am. J. Physiol.*, 1953, *175*, 13–20.
26. PEARSE, A. G. E. Cytochemical demonstration of gonadotropic hormone in human anterior hypophysis. *J. Path. & Bact.*, 1949, *61*, 195–202.
27. PENNYBACKER, J., and RUSSELL, D. S. Necrosis of brain due to radiation therapy. Clinical and pathological observations. *J. Neurol., Neurosurg. & Psychiat.*, 1948, *11*, 183–198.
28. RUSSELL, D. S., WILSON, C. W., and TANSLEY, K. Experimental radionecrosis of brain in rabbits. *J. Neurol., Neurosurg. & Psychiat.*, 1949, *12*, 187–195.
29. SCHOLZ, W., and HSÜ, Y. K. Late damage from roentgen irradiation of human brain. *Arch. Neurol. & Psychiat.*, 1938, *40*, 928–936.
30. TOBIAS, C. A., VAN DYKE, D. C., SIMPSON, M. E., ANGER, H. O., HUFF, R. L., and KONEFF, A. A. Irradiation of pituitary of rat with high energy deuterons. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1954, *72*, 1–21.
31. WARREN, S. Effects of radiation on normal tissues. *Arch. Path.*, 1943, *35*, 121–139 and 305–353.
32. ZEMAN, W. Die Toleranzdosis des Hirngewebes bei der Röntgentiefenbestrahlung. *Strahlentherapie*, 1950, *81*, 549–556.

VOL. 80, NO. 5

RADIATION CHARACTERISTICS OF A KILOCURIE REVOLVING COBALT 60 THERAPY UNIT†

By LAWRENCE H. LANZL, PH.D., *and* LESTER S. SKAGGS, PH.D.
CHICAGO, ILLINOIS

A KILOCURIE cobalt 60 therapy unit designed specifically for revolution therapy has been in use at the Argonne Cancer Research Hospital since early 1954. This unit was designed to obtain the best characteristics which could be achieved at that time without regard to specifications arbitrarily laid down by others.[1]

The unit consists of a single source which can revolve continuously in a vertical plane about a horizontal axis (Fig. 1). A collimated beam of radiation is directed at the axis of revolution. The patient is placed in a recumbent position, on the axis of the machine, and may be treated by full rotational, sectorial, or stationary fields.

One of the unique features of this machine is the use of uranium* rather than other materials for the shield. The result is a large reduction in weight of the shield and consequent decrease in the size and complexity of the machine. Figure 2 shows the relative size of the uranium shield and an equivalent lead shield. The uranium shield weighs 850 pounds; the equivalent lead shield, 3,600 pounds.

Adequate clearance for the patient requires that the collimator be placed at a considerable distance from the patient and thus from the center of revolution; but the collimator then is near the source, resulting in a relatively wide penumbra for the usual extended isotopic sources. Width of the penumbra is not of importance at 250 kv. where it adds its effect to a beam already made diffuse by scattering. In the case of cobalt 60 radiation, scattering is small and excessive penumbra may destroy one of the important advantages of this type of radiation; namely, a sharply defined beam with small integral dose outside the useful region. It is the purpose of this paper to discuss some of the elements of design of the source for the Argonne Hospital machine resulting in a small penumbra, and to show the effect on the radiation characteristics.

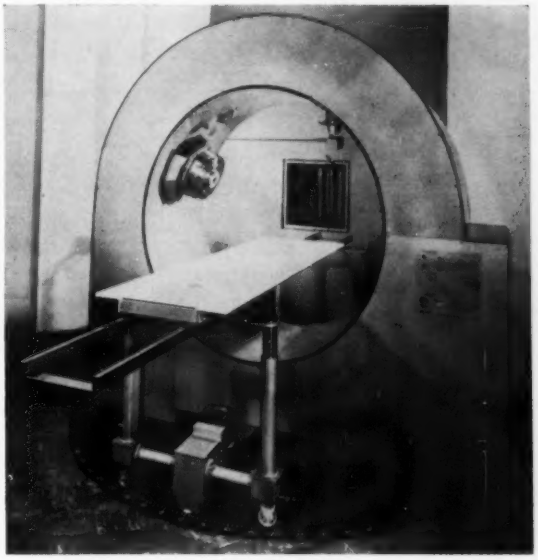

FIG. 1. Cobalt 60 revolution therapy unit showing source shield, treatment cot, and auxiliary control panel.

In order to obtain a small penumbra with a unit of this type, the cross-sectional area of the source, as seen in the direction of the useful beam, should be kept to a minimum. However, in order to have a reasonable dose rate at the tumor site, limits are imposed on the physical size of the source by considerations such as radioactivity required, self-absorption, and problems of production. A reasonable dose rate at the usual tumor distance requires that the ef-

* The material used in the shield was essentially pure uranium. Recent metallurgical developments of uranium alloyed with niobium and zirconium have produced material with a corrosion resistance superior to pure uranium. The density, however, is less than that of uranium.

† From the Argonne Cancer Research Hospital, USAEC, The University of Chicago, Chicago, Illinois. Presented at the Fifty-seventh Annual Meeting of the American Roentgen Ray Society, Los Angeles, California, September 25–28, 1956.

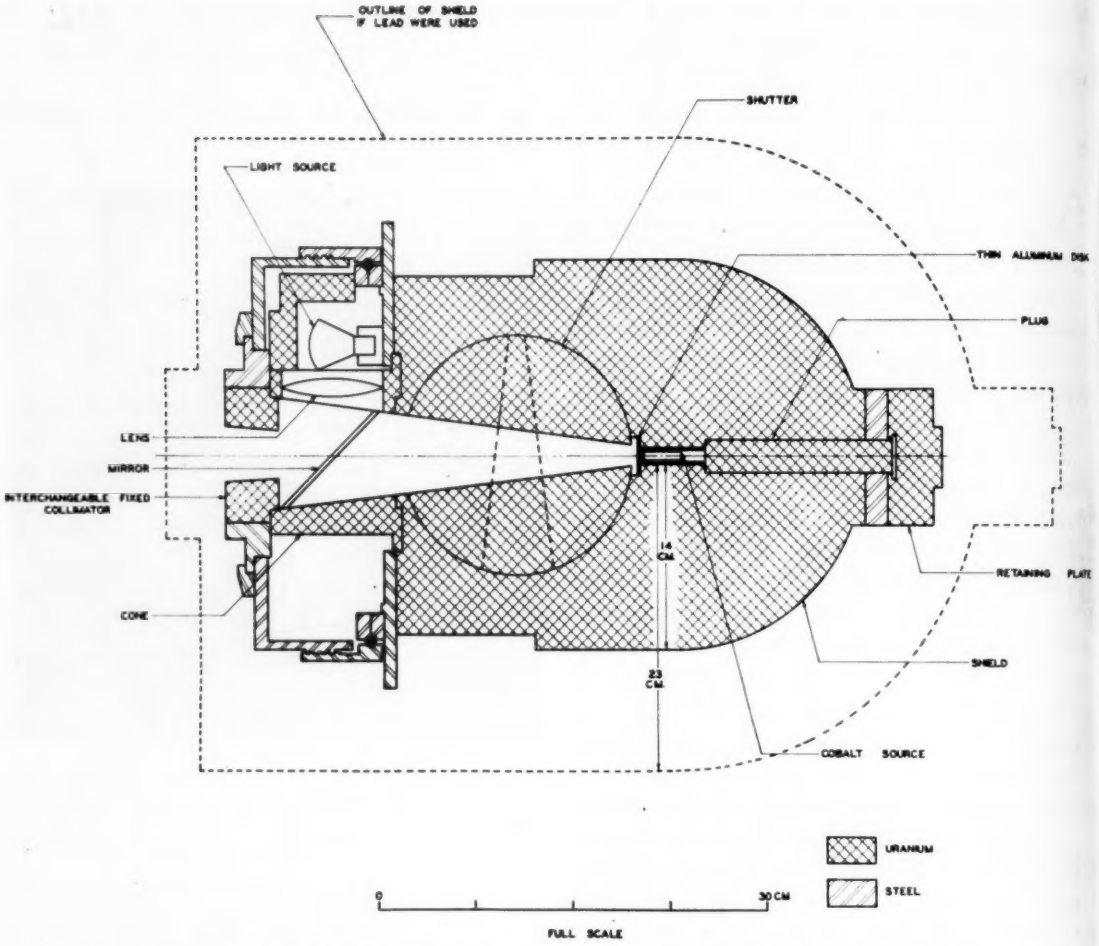

FIG. 2. Cross-sectional sketch of uranium shield showing some of its major components. The outline of a lead shield of comparable radiation absorptivity is superimposed over the actual shield.

fective activity as seen from the front face of the source should be at least 1,000 curies. The total activity of the source depends upon the amount of self-absorption of gamma radiation in the source; *i.e.*, on the thickness of cobalt through which some of the radiation must pass. Figure 3 shows the effect of self-absorption. The upper curve shows the percentage of total radiation which is emitted through the front face of a source as a function of its thickness, and is plotted as length in centimeters. The curves are based on an absorption coefficient, μ, of cobalt 60 gamma rays in cobalt equal to 0.34 cm.$^{-1}$ The second curve, labeled "activity," indicates the total number of curies of activity required of a source if its effective activity as seen from the front face is to be 1,000 curies. The ordinate is read on the left side of the figure. For example, this curve shows that a 3 cm. source of 1,000 curies effective strength would require an absolute activity of 1,640 curies.

The physical size of a source having a given number of curies total activity will depend on the specific activity obtainable in curies per cubic centimeter or, as we have preferred to express it, curies per gram. The lower set of curves in Figure 3 gives the diameter in centimeters of the face of an effective 1,000 curie source versus the thickness in centimeters of that source. The four curves in this set are plotted for

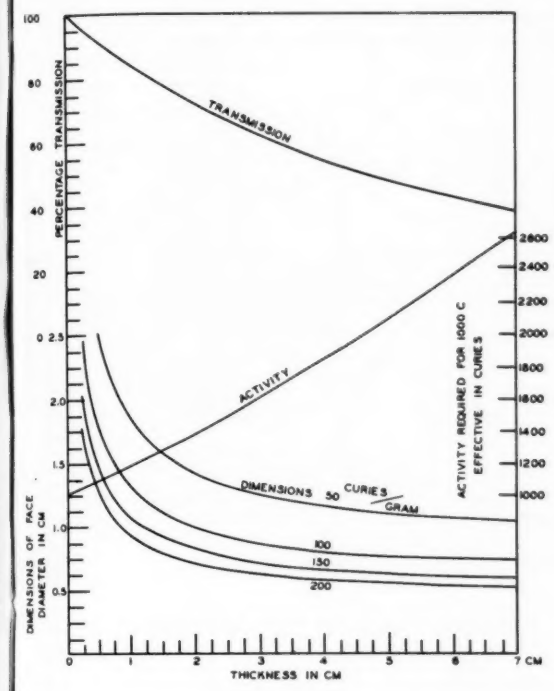

Fig. 3. Effect of self-absorption of cobalt 60 gamma rays in a source. Upper curve shows the percentage of transmission (left side) versus the thickness of the source. Second curve shows the required activity (right side) to obtain an effective 1,000 curie source versus the thickness. The lower set of four curves indicates the specific activity as a parameter with the dimensions of the face diameter (left side) versus thickness.

specific activities of 50, 100, 150, and 200 curies per gram. It is readily seen that in the region of 2.5 cm. diameter, increasing the length slightly results in a drastic reduction of diameter. On the other hand, little reduction of diameter is gained by extending the length of a source to more than 3 cm.

The actual size chosen for the Argonne Hospital source is 3 cm. length and 0.75 cm. diameter. Interpolation from Figure 3 shows that this source size lies at a value of 136 curies per gram for an effective strength of 1,000 curies. The upper curve shows that the effective activity is still 60 per cent of the total activity.

Let us now consider the factors that influence the specific activity. The principal ones are the flux of neutrons in the nuclear reactor and the time of activation. Figure 4 shows the specific activity as a function of time for several values of the neutron flux. These curves assume no effect of self-absorption of neutrons due to the finite size of the source, no burn-up of cobalt 60, and a thermal neutron cross-section of 34.8 barns; but they are corrected for normal decay of cobalt 60 with a half-life of 5.2 years.

At the time when this machine was being designed, the Atomic Energy Commission was completing the Materials Testing Reactor in Idaho. It was expected to produce neutron flux densities as high as 5×10^{14} neutrons per cm.^{2} per second. We see that the required specific activity of 136 curies per gram could be achieved in 0.245 year. However, this does not take into account the practical problems of operating a reactor, of self-absorption of neutrons by the source, or the effect of the source in depressing the neutron flux in its neighborhood. A measurement of the sum of the last two effects indicated a 55 per cent reduction in the effective neutron flux density. As a result, a more reasonable estimate of effective flux density is 1×10^{14} and activation time is 1.33 years.

We now have had practical experience in producing three sources in the Materials Testing Reactor with total activities of 600 curies, 1,200 and 2,800 curies, or specific activities of 50, 100, and 240 curies per gram. The curve for an effective flux density of 10^{14} shows that the first two should have been produced in 0.44 and 0.95 years, respectively. The actual times were 0.93 and 2.18 years, corresponding to an effective flux density of 4.5×10^{13} neutrons per cm.^{2} per second. The third source was produced in three years and two months at an effective flux density of 6.4×10^{13} neutrons per cm.^{2} per second. (The exposure dose rate for this source was 53 roentgens per minute at the center of rotation of the unit.)

A shorter irradiation time can be achieved in the future. Dividing the source during irradiation into 15 disks, each 2 mil-

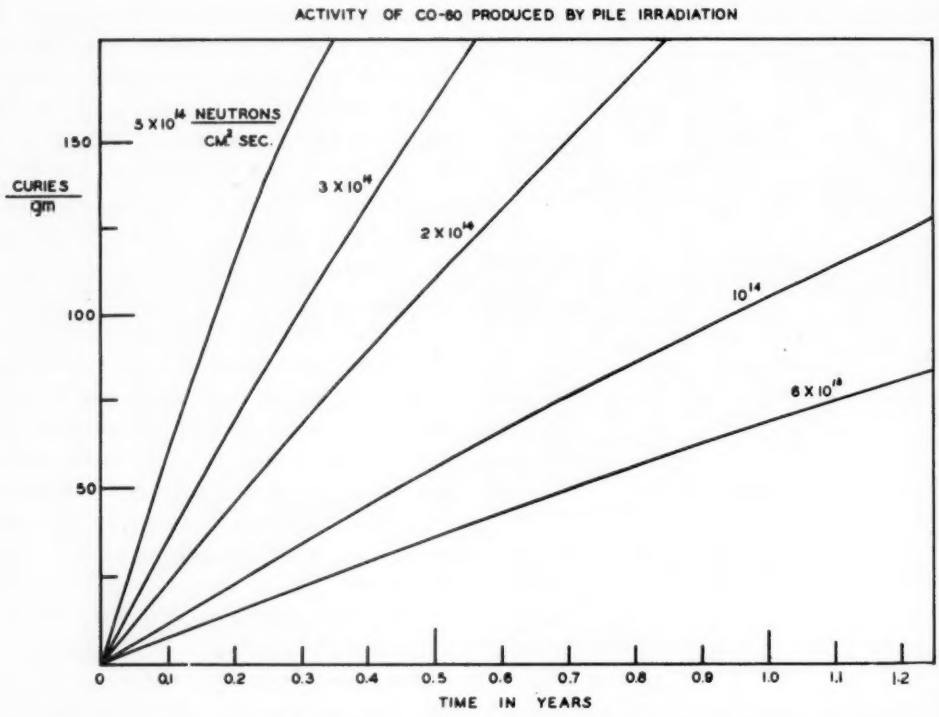

FIG. 4. Plot of specific activity of cobalt 60 from activation of cobalt 59 versus time of activation for neutron flux densities from 6×10^{13} to 5×10^{14} neutrons per square centimeter per second.

limeters thick by 0.75 cm. diameter, and distributing these disks over a volume of about 100 cm.^{3} in the reactor results in a 55 per cent gain of activity.[2] A further improvement also can be expected from the Materials Testing Reactor because of a 33 per cent increase in operating power, which results in a similar increase in neutron flux density.

The effect of the source size just de-

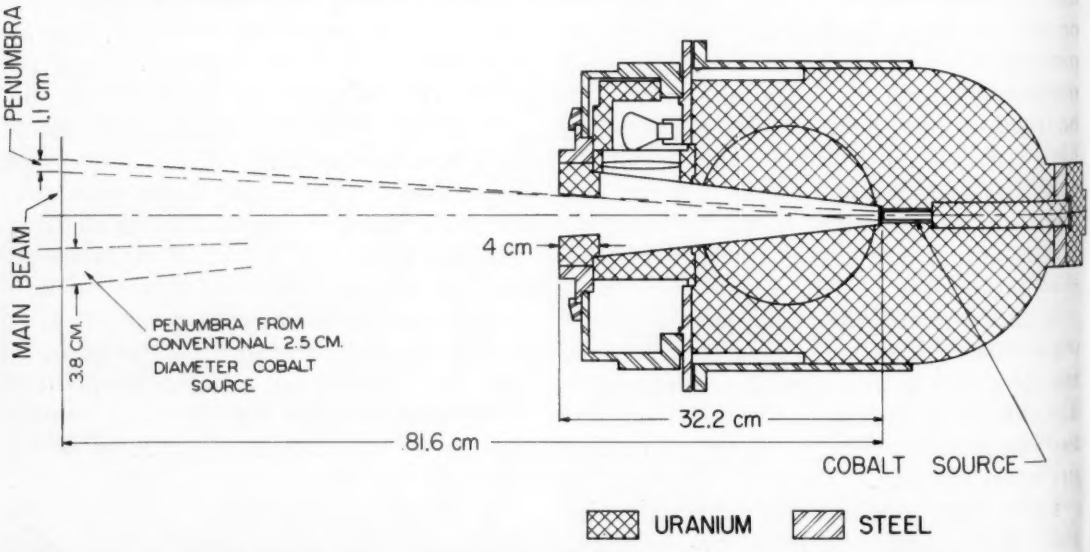

FIG. 5. This sketch shows a 1.1 cm. penumbra from a 0.75 cm. diameter source. For comparison, note the penumbra from a 2.5 cm. diameter source.

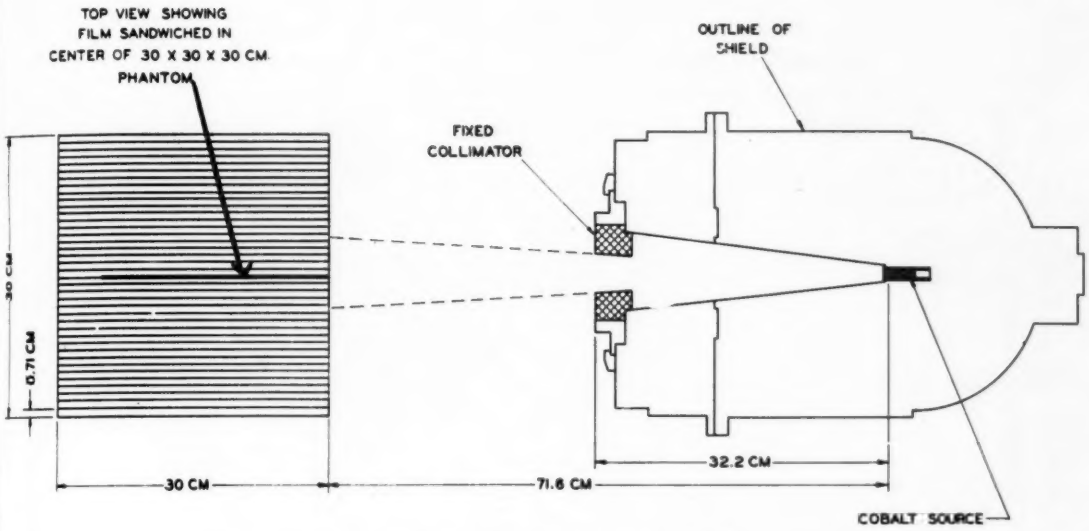

Fig. 6. Experimental arrangement for film response measurements.

scribed on penumbra is shown in Figure 5. With a total source to tumor distance of 81.6 cm., and a collimator to source distance of 32.2 cm., the calculated penumbra is 1.1 cm. In the lower part of the figure, the penumbra which one might expect from a 2.5 cm. diameter source is shown to be 3.8 cm.

Some dose distributions for this unit were determined using a photographic film technique. While a single fixed-beam isodose distribution is more accurately measured using an ion chamber detector, multiple or moving-beam isodose distributions are more easily determined using film, since a moving-beam depth dose distribution can be completely characterized on a single film, whereas only spot measurements are possible with an ion chamber. The present study includes a series of distributions taken with film in circular and elliptically shaped phantoms with a moving beam.

The film response was studied by directing a fixed beam of radiation against a rectangular phantom as shown in Figure 6. The film was placed, in contact, between two sheets of masonite pressdwood of density 1.08. The edges were taped to make the system light-tight, and the resulting film and cassette were placed within a pressdwood phantom. It will be seen that the plane of the film is in the direction of propagation of the gamma-ray beam. The pressdwood sheets of the phantom were clamped together very tightly to eliminate any air pockets at the film which would lead to incorrect results. To test the efficacy of this procedure, a set of films was exposed with the planes of the films and the sheets of pressdwood at right angles to the direction of the beam. The results for the two experimental arrangements were in very close agreement.

The film used was Eastman Industrial A. This film is characterized by a nearly linear relationship between dose and optical density, as the measurements indicate in Figure 7. The effective range of the film is from 1 to 9 roentgens. Each film was developed five minutes in Du Pont 5012 liquid developer at 68° F. under very carefully controlled conditions and read with an Ansco color densitometer. The dose-density curve of Figure 7 was constructed by comparing the density at a given depth along the central axis with the dose as measured with an ion chamber immersed at an equal depth within an identical phantom. The ion chamber was calibrated by the National Bureau of Standards for cobalt 60. The energy degradation of the radiation as it penetrates into the phantom is not taken into account. The entire curve required four different time exposures.

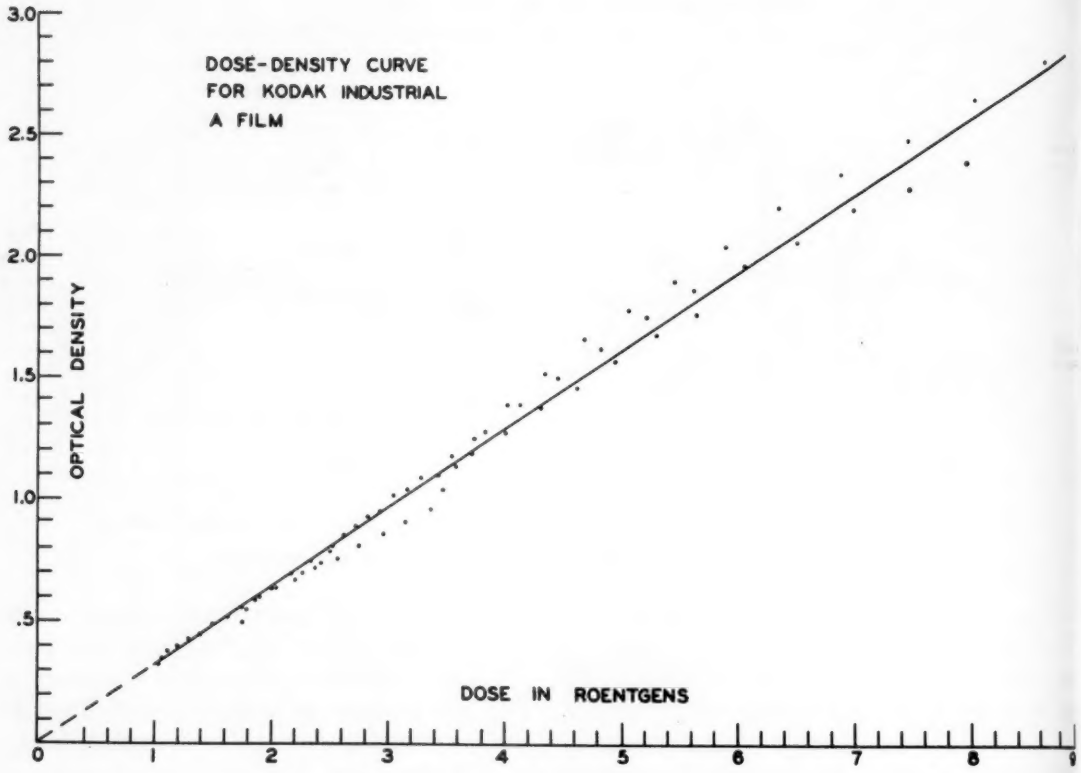

FIG. 7. Dose-density response curve for Kodak Industrial A film.

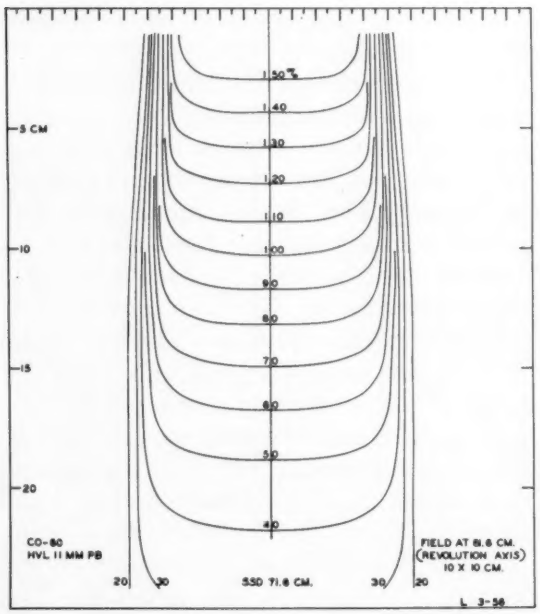

FIG. 8. Isodensity distribution for source to surface distance of 71.6 cm. using Industrial A film. Data are normalized to 100 at 10 cm. depth.

Figure 8 is a complete isodensity curve for a fixed field and rectangular phantom with a source to surface distance of 71.6 cm. The curve is normalized to 100 per cent at a depth of 10 cm. within the phantom, where the field size is 10 cm. × 10 cm. The sharpness of the field is apparent at once. Measurements have shown that the width of the penumbra between 10 per cent and 90 per cent of the central axis dose at a depth of 1 cm. in the phantom is 1.1 cm. These limits were selected by us to define the penumbra; the 10 per cent value is above the normal background of leakage radiation outside the field, and the 90 per cent value is below the variation of dose across the field. (Incidentally, the limits are also those used in electronics to define the rise-time of an amplifier.) The measured values include the effect of scattering as well as the true geometrical penumbra.

The experimental arrangement for film

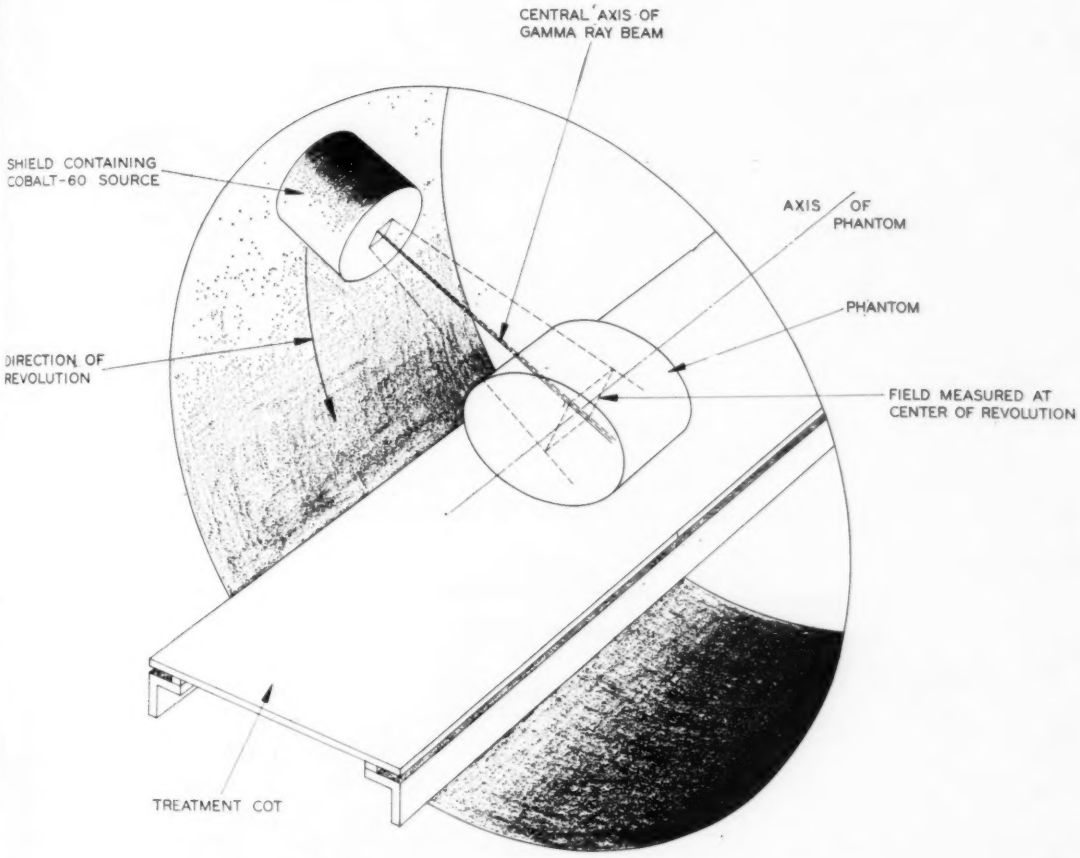

FIG. 9. Experimental set-up for moving beam isodose studies.

dosimetry in the rotational fields is shown in Figure 9. The phantom is elliptically shaped with a major axis of 34 cm. and a minor axis of 24 cm. The plane of the film was the plane of rotation. The time of exposure corresponded to one complete revolution of the source about the phantom, and care was taken to stop the machine exactly at its starting position.

Figure 10 shows the isodensity lines obtained for a 10 by 10 cm. field with the center of rotation at the center of the phantom. The cot with its supporting structure is shown to illustrate its effect on the radiation field. This effect shows up as a distortion of the isodose lines in the vicinity of the cot and support. Near the center of the field, the effect is that of a uniformly distributed absorbing mass over the lower sector of revolution, producing a small upward displacement of the center of the isodose pattern. It should be noted that the radiation falls off rapidly from the tumor volume, and that the surface dose is everywhere less than 40 per cent. The data shown in Figure 7 indicate that an assumption of a simple proportionality between dose and density will result in errors of about 5 per cent. This was verified by separate spot check measurements using Sievert ion chambers on a number of moving-beam distributions. Thus, these distributions can be considered isodose distributions with the 5 per cent accuracy limitation.

The effect of a 5 cm. upward displacement of the center of revolution is shown in Figure 11. There is not much effect on the field in the tumor area, *i.e.*, the area in the vicinity of the highest doses, except for the upward displacement. The dose near the surface is now 60 per cent. (It should be

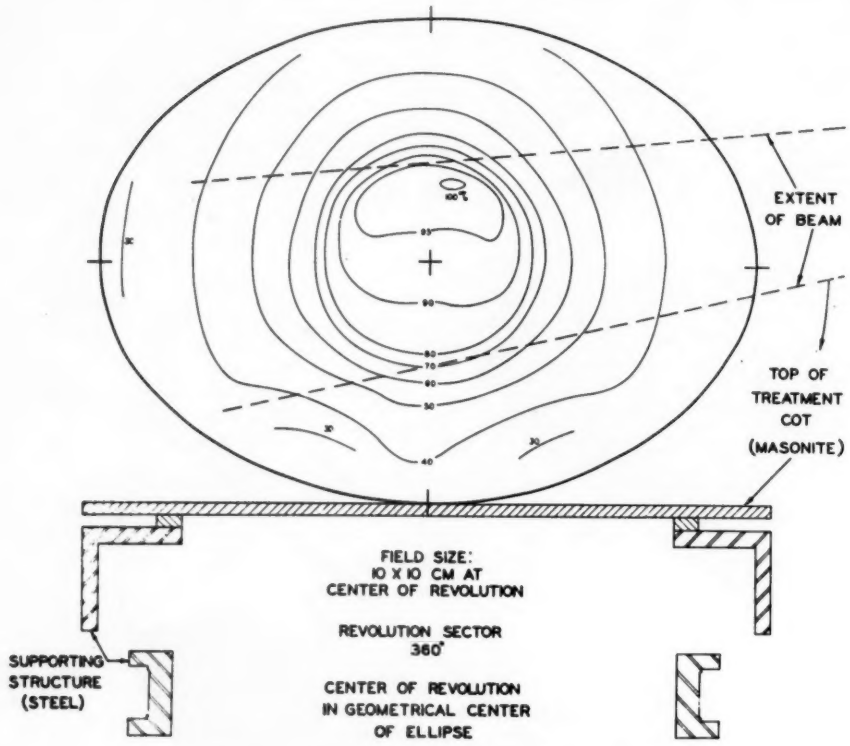

FIG. 10. Moving beam isodose distribution.

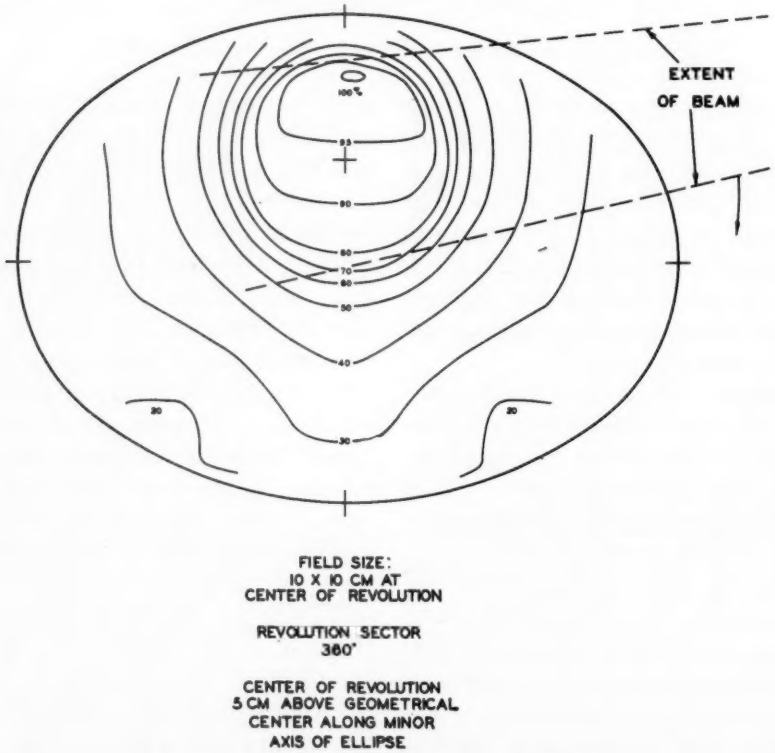

FIG. 11. Moving beam isodose distribution.

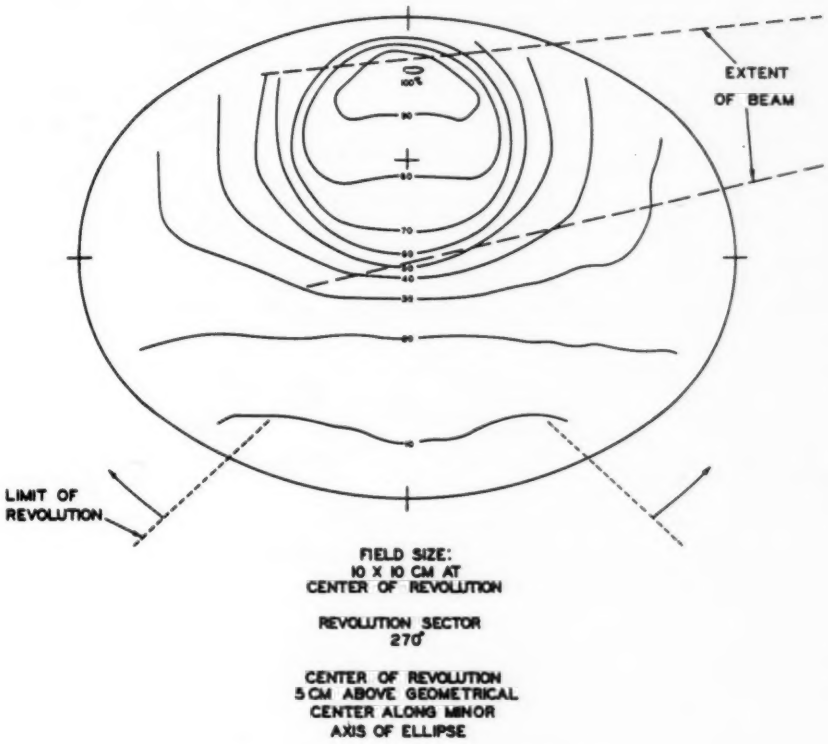

FIG. 12. Moving beam isodose distribution.

remembered that the skin dose is actually less, due to the secondary radiation build-up effect.)

The effect of irradiating the same configuration, but using a 270° sector instead of a complete revolution, is shown in Figure 12. The 90, 80, and 30 per cent isodose lines in this field show that the tumor field has become somewhat flattened and has shifted upward from the center of revolution. Also, the dose in the lower third of the phantom is much reduced.

The isodose distribution for a 4×4 cm. field with complete rotation is displayed in Figure 13. This shows the striking concentration of radiation that can be obtained even in a large cross-section of the body when the penumbra is small.*

A number of other measurements of the radiation characteristics of this machine also have been made. Of these, the central axis tumor-air ratios are probably the most important. These are similar to central axis depth dose data except that the source to tumor distance—or rather the source to ion chamber distance—is fixed, and the thickness of material above is varied. The experimental arrangement is shown in Figure 14. A Victoreen ionization chamber was placed in a pressdwood phantom at the center of revolution of the unit.

Figure 15 shows the results of these measurements. The abscissa shows the thickness of material above the ion chamber; and the ordinate, the ratio of the phantom dose to the air dose. The air dose is measured with the phantom removed. This type of curve is much more useful than the ordinary depth dose curve for calculating dose in revolution therapy, where the distance from the source to the center of rotation is fixed and the distance to the skin varies.

CONCLUSION

This machine has demonstrated that the advantage of small scattering of high ener-

* To date, 18 different rotation and sector distributions have been measured. A sample of these is illustrated in Figures 10, 11, 12 and 13. A limited number of complete sets is available.

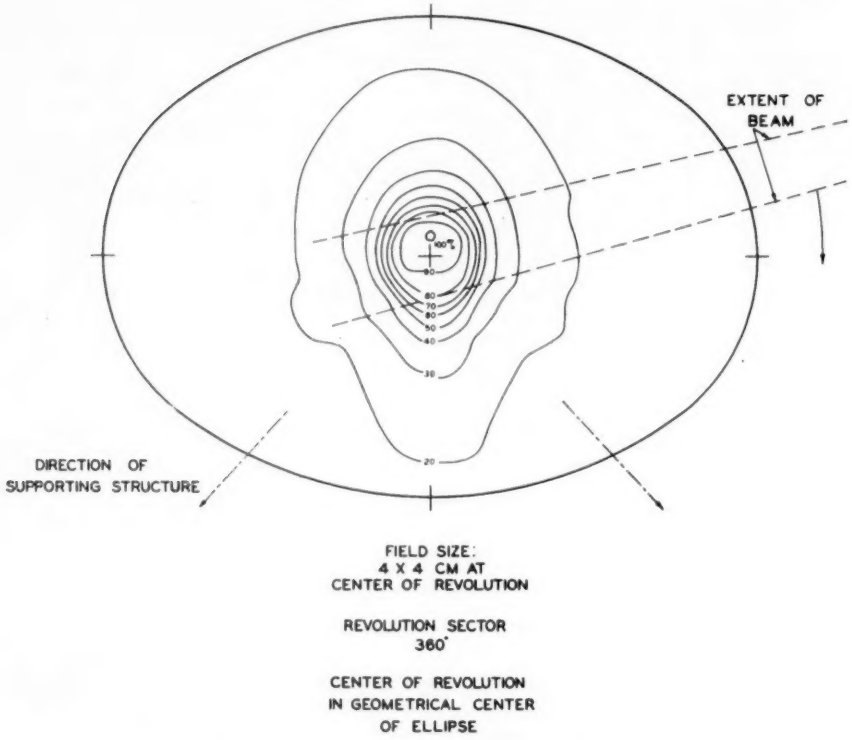

FIG. 13. Moving beam isodose distribution.

gy radiation need not be sacrificed to the large penumbra resulting from the use of extended sources. It has been demonstrated that specific activities in the range of hundreds of curies per gram can be produced. It is easy, with a modest expenditure in self-absorption, to achieve sources of less than 1 cm. diameter, but sources of 0.5 cm. diameter seem outside the range of practical achievement. It is evident from

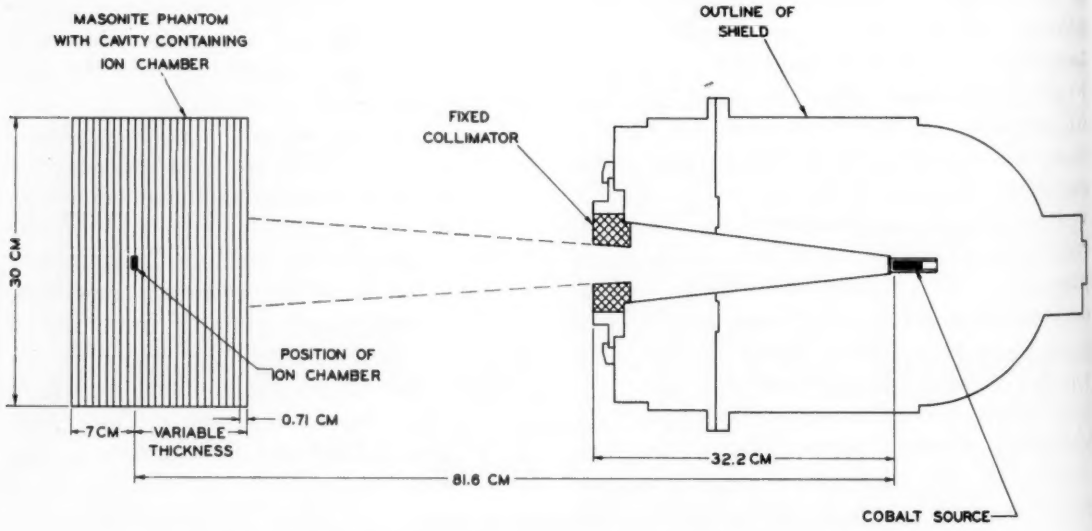

FIG. 14. Experimental arrangement for target-air ratio measurements with fixed source to detector distance.

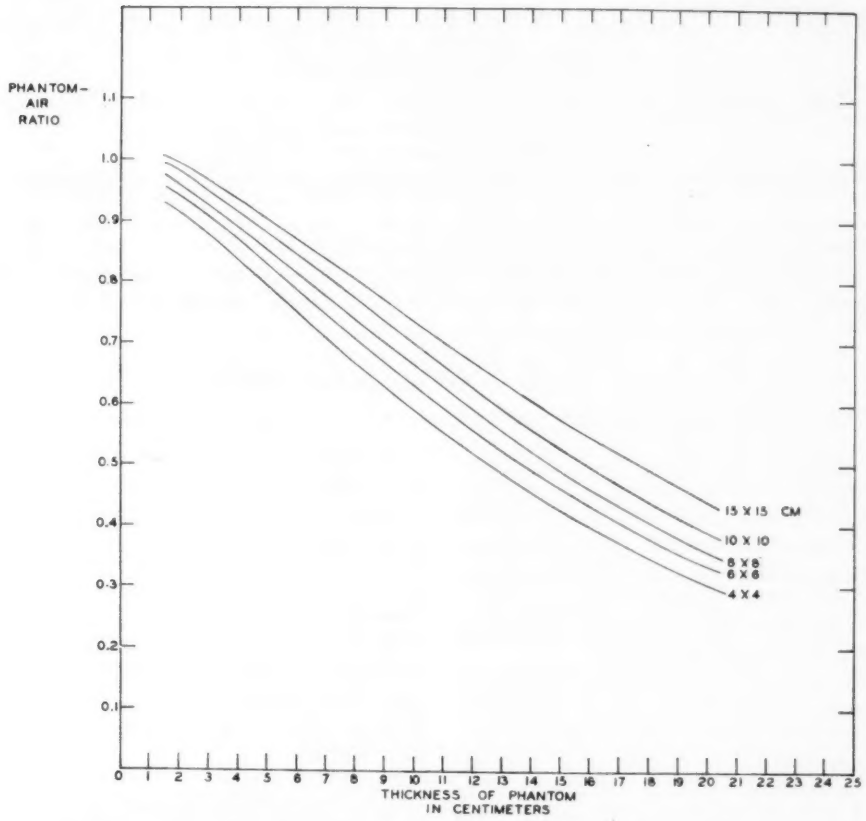

FIG. 15. Tumor (or phantom) dose to air dose ratio versus thickness of phantom for a fixed source to detector distance.

the single beam isodose distributions that a small penumbra was indeed achieved. Significant differences in distribution are obtained by changing from complete rotation to sector rotation. Depth dose distributions for moving beams of small cross-section (*i.e.*, where the cross-section is small compared to the size of the phantom) show a very rapid fall-off of dose outside the tumor region. As the cross-section of the beam approaches that of the phantom, this fall-off becomes less steep.

Lawrence H. Lanzl, Ph.D.
The University of Chicago
950 East 59th Street
Chicago 37, Illinois

The authors wish to thank Dr. W. A. Jennings and A. L. McCrea for carrying out some of the Sievert chamber measurements.

REFERENCES

1. LANZL, L. H., DAVISON, D. D., and RAINE, W. J. Kilocurie revolving cobalt-60 unit for radiation therapy. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1955, *74*, 898–916.
2. LANZL, L. H., and SKAGGS, L. S. Irradiating smaller pieces gives stronger Co^{60} sources. *Nucleonics*, 1956, *14*, No. 1, 66; also, Neutron flux depression and self-protection considerations in activation of cobalt-60 for use in moving beam therapy. Argonne Cancer Research Hospital, Semi-Annual Report, March, 1956, No. 5, p. 69.

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

Editor: LAWRENCE REYNOLDS, M.D.

Associate Editors: HARRY HAUSER, M.D., TRAIAN LEUCUTIA, M.D., RUSSELL H. MORGAN, M.D., EDWARD B. D. NEUHAUSER, M.D., WENDELL G. SCOTT, M.D.

Consulting Editorial Board: See front cover.

Published by: CHARLES C THOMAS, PUBLISHER, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued monthly. Annual subscription: United States, Mexico, Cuba, Central and South America, $15.00; Canada, $16.00; other countries, $17.00. Current single numbers, $1.50. Advertising rates submitted on application. Editorial office, 110 Professional Building, Detroit 1, Michigan. Office of publication, 301–327 Eas Lawrence Avenue, Springfield, Illinois. Information of interest to authors and readers will be found on page vi

Officers and Standing Committees

AMERICAN ROENTGEN RAY SOCIETY

President: Wendell G. Scott, St. Louis, Mo.; *President-Elect:* Barton R. Young, Philadelphia, Pa.; *1st Vice-President:* John P. Medelman, St. Paul, Minn.; *2nd Vice-President:* John E. Whiteleather, Memphis, Tenn.; *Secretary:* C. Allen Good, Mayo Clinic, Rochester, Minn.; *Treasurer:* Robert K. Arbuckle, Samuel Merritt Hospital, Hawthorne and Webster Sts., Oakland 9, Calif.

Executive Council: W. G. Scott, B. R. Young, J. P. Medelman, C. A. Good, R. K. Arbuckle, Lawrence Reynolds, L. W. Paul, H. M. Stauffer, Cesare Gianturco, W. E. Chamberlain, P. C. Hodges, J. C. Cook, R. C. Pendergrass, R. M. Caulk, J. F. Holt, A. E. Childe, Wilbur Bailey, Chairman, 2009 Wilshire Blvd., Los Angeles, Calif.

Program Committee: C. A. Good, Rochester, Minn., H. M. Stauffer, Philadelphia, Pa., Lawrence Reynolds, Detroit, Mich., Cesare Gianturco, Urbana, Ill., Wilbur Bailey, Los Angeles, Calif., H. O. Peterson, St. Paul, Minn., B. R. Young, Chairman, Philadelphia, Pa.

Publication Committee: E. B. D. Neuhauser, Boston, Mass., H. G. Reineke, Cincinnati, Ohio, V. P. Collins, Houston, Texas, J. F. Roach, Albany, N. Y., H. M. Stauffer, Chairman, Philadelphia, Pa.

Finance and Budget Committee: S. W. Brown, Augusta, Ga., J. F. Holt, Ann Arbor, Mich., A. E. Childe, Winnipeg, Manitoba, Edward L. Jenkinson, Chicago, Ill., L. W. Paul, Chairman, Madison, Wis.

Committee on Scientific Exhibits: T. F. Leigh, Emory University, Ga., R. H. Marshak, New York, N. Y., Cesare Gianturco, Chairman, Urbana, Ill.

Representatives on the American Board of Radiology, H. D. Kerr, St. Michaels, Md., T. Leucutia, Detroit, Mich., C. A. Good, Rochester, Minn.

Director of Instructional Courses: H. O. Peterson, St. Paul, Minn., *Manager of Annual Meeting:* James C. Cook, 110 Professional Building, Detroit 1, Mich.

Editor: Lawrence Reynolds, 110 Professional Building, Detroit 1, Mich

Fifty-ninth Annual Meeting: Shoreham Hotel, Washington, D. C., September 30–October 3, 1958.

AMERICAN RADIUM SOCIETY

President: Milford D. Schulz, Boston, Mass.; *President-Elect:* Theodore R. Miller, New York, N. Y.; *1st Vice-President:* Theodore P. Eberhard, Ann Arbor, Mich.; *2nd Vice-President:* James F. Nolan, Los Angeles, Calif.; *Secretary:* Robert L. Brown, P. O. Box 459, Emory University, Ga.; *Treasurer:* Jesshill Love, 234 Medical Arts Bldg., 1169 Eastern Parkway, Louisville, Ky.

Executive Committee: Grant H. Beckstrand, Chairman, Long Beach, Calif.; Norman A. McCormick, Windsor, Ontario, Canada; Ralph T. Ogden, Hartford, Conn.

Program Committee: Milford D. Schulz, Chairman, Boston, Mass.; Lloyd F. Craver, New York, N. Y.; Morton M. Kligerman, New York, N. Y.; Elizabeth F. Focht, New York, N. Y.; J. Samuel Binkley, Oklahoma City, Okla.; Justin J. Stein, Los Angeles, Calif.; William S. MacComb, Houston, Texas; Theodore R. Miller (ex officio), New York, N. Y.

Publication Committee: Harry Hauser, Chairman, Cleveland, Ohio; Martin Van Herik, Rochester, Minn.; J. Robert Andrews, Bethesda, Md.

Public Relations Committee: Henri LeClaire, Chairman, Cincinnati, Ohio; John V. Blady, Philadelphia, Pa.; Harold E. Johns, Toronto, Ontario, Canada.

Janeway Lecture Committee: Gioacchino Failla, Chairman, New York, N. Y.; H. Dabney Kerr, St. Michaels, Md.; Lloyd F. Craver, New York, N. Y.

Representatives on the American Board of Radiology: Douglas Quick, New York, N. Y.; B. P. Widmann, Philadelphia, Pa.; Frederick W. O'Brien, Boston, Mass.

Representatives on the National Committee on Radiation Protection: Edith H. Quimby, New York, N. Y.; Theodore P. Eberhard, Ann Arbor, Mich.

Representative on the Board of Chancellors of the American College of Radiology: Charles L. Martin, Dallas, Texas.

Committee on Arrangements: Charles C. Stetson, Chairman, Englewood, N. J.; Henri LeClaire, Cincinnati, Ohio; Victor A. Marcial, Puerto Rico; Howard H. Ashbury, Charlottesville, Va.; Jesshill Love, Louisville, Ky.

Forty-first Annual Meeting: The Homestead, Hot Springs, Virginia, April 6–8, 1959.

Vol. 80, No. 5

EDITORIAL

ETYMOLOGIC AND OTHER ASPECTS OF PALLIATION

> If the changes that we fear be thus irresistible, what remains but to acquiesce with silence, as in the other insurmountable distresses of humanity? It remains that we retard what we cannot repel, that we palliate what we cannot cure.
>
> Samuel Johnson

THE incidence of neoplasms is on the increase because of the advancing biologic and median age of civilized persons. As long as the perfect oncolytic agent is wanting, the number of "hopeless cancer" patients will also continue to rise. Another distressing consequence, felt literally by the growing number of those who require specialized oncologic attention, is the fact that they can hardly be accommodated with the facilities heretofore in operation. In the modern version of the struggle for life, tangible results are no longer a prerequisite for continued interest and support. When properly exhibited to the public eyes and ears, the lack of effective treatment for a disease with strong emotional appeal can motivate repeatedly successful campaigns to collect funds for research and ancillary care. Academic curricula, however, do not necessarily reflect the trends of current publicity strategy; thus in medical schools not enough hours of formal teaching are specifically devoted to the management of "incurable" conditions. As a result, many a physician experiences a feeling of inadequacy and despair when he must approach a patient in whom, as in the metaphor of Metastasio,[1] "the canker which the trunk conceals, is revealed by the leaves, the fruit, or the flower."

Palliation is a delicate and complex art. It cannot offer the "scientific" incentive of the presumed (or rather desired) completeness of an evisceration, nor does it promise spectacular results, although at times it may achieve them unexpectedly. It is fundamentally wrong to believe that when a patient has been declared "incurable" he has passed the point of no return, and cannot be further harmed, in the same way in which infinity cannot grow any bigger, regardless how many finite quantities are added to it. The basic philosophy of palliation is built upon the realization that human suffering is never infinite. It can always grow a little worse, and hurt a little stronger than the day before, until the very end. Considerable clinical judgment, technical proficiency, and personal experience must be accumulated to perform successfully in a field which encroaches upon the borderlines of so many specialties. Another requirement is individualization of approach, which has been stressed everywhere in medicine but which nowhere can be as essential as when a single overdosage can irremediably destroy the fleeting benefits of a carefully planned and executed program. Lastly, and most important of all, the patient's own problems and sufferings must be met with continuous warmth and sympathetic understanding, never to be stained, not even with a trace of wrongly displayed commiseration.

Medical historians have demonstrated that theoretic principles are more easily grasped after linguistic identification of the catchwords used in their definition. Moreover, etymologic analysis, with its synonyms and analogies, provides a fascinating insight into the many ways in which cognate meanings can create strange associations of ideas. In the case of palliation, the primary word or etymon was the Latin

[1] Literary pseudonym of A. D. B. Trapassi (1698–1782).

word pallium, which meant a loose mantle or cover, a much simpler and less formal attire than the toga.

The English verb palliate comes from the Latin palliare, which originally meant to cover with or as with a cloak.[2] As time went on, three main groups of synonymies developed, the earliest of which evolved round the sense of hiding, *i.e.*, (1) to palliate was to put out of sight, or beyond ready observation or approach, that is to hide, cloak, cover up, conceal, disguise, veil, screen. Within the significance of medical palliation, this includes the various prosthetic devices intended to replace functionally (speech, breathing, eating), or at least esthetically, the necrotized and/or excised portions of skin, muscle, or bone from the face and other parts. As a corollary may be considered the fact that all patients must maintain, as long as practicable, an acceptable outward appearance (clothing, smile, make-up), because this will improve their inward look at the same time. Another analogy of the verb hide is to shelter, which implies giving temporary cover from something that might harm. Patients may sometimes be given actual refuge in adequate (not only custodial) facilities, but to shelter means also to protect them from the cruel knowledge of their irremediable condition. In this respect, one cannot cloak (which means to hide completely as behind a pall), just palliate (that is to veil or screen so as to make the outlines indistinct). The patient who harbors an incurable malignancy must be told he is seriously ill, the nature of his illness being then described as either (a) non-neoplastic (any popular disease with similar symptomatology), (b) benign growth (with details concerning the severity of local extensions), or (c) malignant tumor (never cancer, and always amenable to therapy). The degree of disclosure shall be adjusted to the patient's personality. He is entitled to the benefit of doubt; one may always downgrade at first, and preserve another step of revelation for a later date when added symptomatology will require further explanations. There are very few individuals who can or should be forewarned of their impending death (even then, the cold facts must be palliated with the theoretic chance of future stabilization) for, as Keats once wrote, "to bear all naked truths, and to envisage circumstance, all calm, is the top of sovereignty."

The next group of synonyms is based on the sentence that (2) to palliate is to cover with a mantle of excuses. When we palliate a wrong, we seek to extenuate it in part. Either to palliate or to extenuate is to admit the existence of the evil under consideration, but to extenuate is rather to apologize for the offender, while to palliate is to disguise it (circumstances which cannot change the inherent wrong may be extenuating, can never be palliating). These meanings can be applied to the numerous half-truths proffered in reply to very pointed questions asked in the course of the treatment of advanced malignancies. Since the duration of the final phase can extend over several years, it takes much inventiveness, common sense, and experience to find the right words. It may even be desirable to formulate standard answers to certain, often heard queries, partly because patients discuss their problems between themselves, and also to prevent contradictions during later interviews. For the same reason it may be worthwhile to incorporate in the records any unusual euphemisms offered to the patient, as this will save the time and brainwork needed to reassure him after the discovery of inconsistencies in subsequent comments. The accomplished therapist knows that the right word at the right time is more effective than one sixth of morphine, while the loss of hope proves to be, in Milton's words, "as killing as the canker[3] to the rose."

[2] Cloak is a transliteration from the Old French *cloke*, akin to the Medieval Latin *clocca*, the bell (*Glocke* in German), in the sense of wide, shapeless garment.

[3] In Cromwell's England, *canker* meant a plant disease, the dog-rose, the canker-worm, and the fourth zodiacal constellation, as well as cancerous ailments in humans. The word comes from the Latin *cancer* (crabfish) which, according to Galenus (*De art. curat., lib. 2, cap. 11*), was selected because the dilated veins surrounding an indurated breast tumor resemble the hard claws and

The last and largest group of synonyms revolves around the strictly medical connotation that (3) to palliate is to diminish the violence of a disease. In this sense the term means (a) to alleviate, that is to lift a burden, or at least to lighten it, and thus make it more bearable, which is less than to relieve a sufferer, and certainly less than to remove the cause of suffering; (b) to allay or to lay to rest: for instance, we allay suffering by using means to soothe that which is excited, or otherwise appease, pacify, mollify, assuage, calm, quiet, still, or in one word, tranquilize. Among the cognates of soothing is to solace, console, comfort, sympathize, which in turn contain meanings easily blended into those expounded hereunto; (c) to mitigate or to make milder or less severe, such as to moderate, lessen, attenuate, decrease, abate, or reduce. (It may be stated parenthetically that many of these analogies have somewhat of a provisorial or transient character, similar to the effectiveness of today's cytostatics, *e.g.*, triethylene melamine in Hodgkin's disease.) The above array of terms covers every possible facet of medical palliation from the analgesic roentgen therapy[4] administered to lessen the pain of bone metastases to posterior rhizotomy, the purpose of which is to suppress or at least to attenuate intractable pain; from radioactive colloidal Au^{198} (or nitrogen mustard) instilled intraperitoneally to lighten the burden of ascites to bypass operations, performed to relieve mechanical bowel obstruction of malignant origin; and from the blood transfusions given to allay the dyspnea of a leukemic patient with anemia to the supervoltage radiation therapy which alleviates dysphagia by reopening an esophagus encroached upon by carcinoma. And since most of the patients have both "the canker, and the grief" (Byron), their anxiety must be mitigated, *i.e.*, tranquilized—a task which has been facilitated by recent pharmacologic advances.

It is difficult to establish a firm set of rules which could apply to each individual case, but, perhaps, a tentative decalogue of palliation would help in providing a basic philosophy for the management of incurable patients afflicted with malignant neoplasms or diseases:

1. Only one physician shall be in charge of a patient. Other consultants might be called in to help in the evaluation and care of a case, a surgeon might be asked to perform a certain procedure, a dentist could extract a few teeth, but the over-all responsibility for the treatment of the patient's body and mind must be in the hands of one physician only.

2. The intent of palliation shall be kept in focus. Iatrogenic drug addiction should not be permitted to occur, except in the last months of life expectancy, when it may become desirable.

3. A patient shall have an adequate period of respite from treatment. It is good medical practice to intercalate between periods of active treatment, intervals of rest during which injections, medication and strict diets are discontinued. This will make for easier handling of the patient's morale.

4. The patient shall not sense deprecation of his previous treatment. It is of no help to the patient to let him know that treatment might have been easier, or more successful, had he come earlier.

5. As a rule, nothing beyond supportive therapy shall be given to a comatose patient known to have an incurable malignancy.

6. The meaning of palliation shall not be adulterated. Besides aiming to prolong life,

---

round body of the European variety of crab (*C. pagurus*). Cancer is actually the literal translation into Latin of the Greek term *karkynos*, whence carcinoma is derived from *καρκίνος*, crab and *νέμειν* or *νομή*, to spread by eating around. The vocable is used in the famous aphorism (6: 38) in which Hippocrates suggested that (over) treatment in cases of crypto-carcinoma (occult or internal malignancy) may shorten, rather than prolong, the patient's life. This evolved later into the doctrine of *Noli me tangere*, applied often as a warning not to operate *ulcus rodens*, a variety of basal-cell carcinoma of the skin, which almost never metastasizes.

[4] Every attempt must be made to control pain, but chemical analgesia should be used sparingly, at least until all other measures, from regional novocain infiltrations to lobotomy, if indicated, have been exhausted. Large doses of opiates are indicated only when it becomes advisable to produce a clouded state of mind.

all efforts should be made to improve the patient's comfort. As an example, if the terminal stages of carcinomatous extension in a case in which the primary tumor was located in the uterine cervix are accompanied by uremia with a clouded sensorium, ureterostomy for ureteral drainage should be weighed with regard to life expectancy in each particular case and decided upon on its own merits or demerits.

7. The patient shall be given the opportunity to make his own decisions. This is especially true when the projected extensive removal of organs will result in the artificial drainage of excreta, and in other consequences leading to invalidism. Even in less compulsory situations, the expected degree of disability and inconvenience of a palliative procedure must be sincerely explained to the patient and the final decision should be his.

8. The patient's peace of mind shall be protected. Information regarding his illness should be offered to the patient only to the extent of his understanding and receptivity. Beyond that, proper therapy should be directed to the psychosomatic aspects of advanced malignancies.

9. The patient's family life shall be protected. As long as feasible, the patient should be encouraged to live in his familiar environment, continue his occupation and keep on enjoying his hobbies. The family should be told the truth about the patient's condition, but a divulgence of all the details to the spouse is not recommendable, at least not in the majority of cases.

10. The patient's economic status shall be considered. Sincere appraisal of the situation and a frank discussion with a responsible relative (or friend of the family) will help in bringing forth the proper decisions.

But then, in a larger sense, one may be tempted to inquire whether palliation is worth all these efforts. This utilitaristic query could only be answered by compiling a list of various levels of human suffering. In the meantime, a growing number of people will demand and require the impalpable, immeasurable, but nonetheless very real benefits of palliation.

Certainly, early detection gives a better chance to obtain favorable therapeutic results, but it cannot always insure them. Often, when the patient was able to reach a relatively advanced stage before the appearance of symptoms, his chances of prolonged survival are better than those of another patient in whom the first symptoms have appeared during the early phases of tumor growth. This rule, which is consistent with Ian Macdonald's concept of the biologic predetermination of neoplastic development, can be confirmed in everyday practice, time and again. It becomes particularly evident in lymphomata, and especially in the so-called follicular variety, which has therefore been labeled "benign" by a wishful thinker. Cases which enter this category have been maintained in fairly good health for ten or twenty years after obtaining the histologic proof of the disease. Judicious council and adequate therapeutic efforts can keep many of these "hopeless" patients afloat for long intervals of time. And since all humans are mortal, there is in essence only a quantitative, not a qualitative difference between the results obtained in "curable," and the results obtained in "incurable" patients, *i.e.*, the survival time. From this vantage point, palliation acquires a deeper meaning, and grows in stature, so that if all nosologic entities could be simplified to a common denominator, one might agree with the immortal G. B. Shaw, that "the only difference between one man and another is the stage of the disease at which he lives."

E. R. N. Grigg, M.D.
Department of Radiology
Cook County Hospital
Chicago 12, Illinois

SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Sept. 30–Oct. 3, 1958.

American Radium Society
Secretary, Dr. Robert L. Brown, P.O. Box 459, Emory University, Ga. Annual meeting: The Homestead, Hot Springs, Va., April 6–8, 1959.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: Palmer House, Chicago, Ill., Nov. 16–21, 1958.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Feb. 4–7, 1959, Chicago, Ill.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual meeting: June 8–12, 1959, Atlantic City, N. J.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. Fall 1958 Meeting and Examinations Dec. 8–12, inclusive, Washington, D. C. Final date for filing applications was July 1, 1958. Special Examination in Nuclear Medicine for those diplomates in Radiology and Therapeutic Radiology, December 6, 1958, Washington, D. C.; deadline for filing applications was October 1. Special Spring Examination, March 16–19, 1959, Cincinnati, Ohio; deadline for filing applications is November 1, 1958. Candidates completing training June 30, 1959 are not eligible for the Spring 1959 examinations.

Ninth International Congress of Radiology
Secretary-General, Dr. Hans v. Braunbehrens. Request for information should be addressed to Dr. Viktor Loeck, Kongressbüro, Forsthausstrasse 76, Frankfurt am Main, Germany. Meets in Munich, Germany, July 23 to July 30, 1959.

Sixth Inter-American Congress of Radiology
Secretary for North America, Dr. Jorge de la Flor, Hospital Arzobispo Loayza, Lima, Perú. Meets in Lima, Perú, Nov. 2–8, 1958.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill. Winter meeting, Sheraton-Cadillac Hotel, Detroit, Mich., Dec. 8–10, 1958.

Arizona Radiological Society
Secretary, Dr. R. Lee Foster, 1313 N. Second St., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. E. A. Mendelsohn, Holt-Krock Clinic, Fort Smith, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. Paul Riemenschneider, Medical College, State University of New York, Syracuse, N. Y. Annual meeting: Spring, 1959 in Atlanta, Ga.

Atlanta Radiological Society
Secretary, Dr. J. L. Clements, Jr., 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St., Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. George A. Manfredonia, One Hanson Place, Brooklyn, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Charles Bernstein, 685 Delaware Ave., Buffalo 9, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. George B. Cahill, 802 Burns Ave., Flossmoor, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Frederick A. Rose, 2065 Adelbert Rd., Cleveland 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Lorenz R. Wurtzebach, 601 E. Nineteenth Ave., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. Paul J. Kingston, 114 Woodland St., Hartford, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Club
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Joseph O. Reed, Jr., Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Eastern Radiological Society
Secretary, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio.

Florida Radiological Society
Secretary, Dr. C. Robert DeArmas 135 Broadway,

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga. Meets Spring and Fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. George P. Daurelle, Jackson Memorial Hospital, Miami 36, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles J. Cherre, 462 N. Taylor, St. Louis 8, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Edward B. Singleton, 6621 Fannin St., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles R. McWilliams, Magic Valley Memorial Hospital, Twin Falls, Idaho. Meets annually at same time as Idaho State Medical Association.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. C. A. Stayton, Jr., 313 Hume-Mansur Bldg., Indianapolis 4, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. James R. Stark, 3244 E. Douglas, Wichita, Kansas. Meets in spring with State Medical Society, and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. Robert H. Akers, 1405 West Broadway, Louisville 3, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. C. P. Naidorf, 411 Parkside Ave. Brooklyn 26, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Robert B. Engle, St. Luke Hospital, Pasadena, Calif. Meets second Wednesday of month in September, November, March, April and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY
Secretary, Dr. Francis J. O'Connor, Augusta General Hospital, Augusta, Maine. Meets in June, September, December and March.

MARYLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

MEMPHIS ROENTGEN SOCIETY
Secretary, Dr. James L. Booth, 899 Madison Ave., Memphis 3, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY
Secretary, Dr. Robert P. Henderson, 316 Medical Arts Bldg., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY
Secretary, Dr. Arthur T. Austin, 104 The Doctors Bldg., Billings, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY
Secretary, Dr. Jerome Zwanger, 126 Hicksville Rd., Massapequa, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. John E. Gary, 1180 Beacon St., Brookline 46, Mass. Meets third Friday of each month, October through May, at The Longwood Towers, Brookline, Mass.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. Harold G. Jacobson, 210th St. and Bainbridge Ave., New York 67, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 4:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville 4, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

OHIO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Francis C. Curtzwiler, 421 Michigan St., Toledo 2, Ohio. Annual meeting: Cincinnati, Ohio, May, 1959.

OKLAHOMA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Edmond H. Kalmon, Jr., 300 Northwest 12th Street, Oklahoma City, Okla. Three regular meetings annually.

OREGON RADIOLOGICAL SOCIETY
Secretary, Dr. C. V. Allen, Veterans Hospital, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. Robert W. Hanf, 900 S. Auburn, Kennewick, Wash. Meets annually in May.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State St., Harrisburg, Pa. Annual meeting: Harrisburg, Pa., April 24–25, 1959.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia 4, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edwin Beck, 3500 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenley Restaurant.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Ted F. Leigh, Emory University, Georgia. Annual meeting: New Orleans, La., Nov. 3–6, 1958.

Radiological Society of Greater Cincinnati
Secretary, Dr. Warner Peck, Carew Tower St., Cincinnati 2, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Robert G. Rigler, Straub Clinic, 1020 Kapiolani St., Honolulu 14, Hawaii. Meets third Monday of each month alternately at 4:30 P.M. and 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. Samuel B. Chapman, Jr., 830 Argyle Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. Andrew P. Dedick, Jr., 67 E. Front St., Red Bank, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting: To be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Harold P. Tompkins, 658 S. Westlake, Los Angeles 57, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. John W. Colgan, 277 Alexander St., Rochester 18, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: To be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Irma Smith, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Ralph J. Littwin, Bristol Hospital, Bristol, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Charles E. Bickham, Jr., 1835 Eye St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

Society of Nuclear Medicine
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. Annual meeting: To be announced.

South Bay Radiological Society
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. Wayne Reeser, 804 Burroughs St., Conway, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. J. E. Miller, 3500 Gaston Ave., Dallas 10, Texas. Next meeting January 30 and 31, 1959, Statler-Hilton Hotel, Dallas, Texas.

Tri-State Radiological Society
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June. at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga. Meets Spring and Fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. George P. Daurelle, Jackson Memorial Hospital, Miami 36, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles J. Cherre, 462 N. Taylor, St. Louis 8, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Edward B. Singleton, 6621 Fannin St., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles R. McWilliams, Magic Valley Memorial Hospital, Twin Falls, Idaho. Meets annually at same time as Idaho State Medical Association.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. C. A. Stayton, Jr., 313 Hume-Mansur Bldg., Indianapolis 4, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. James R. Stark, 3244 E. Douglas, Wichita, Kansas. Meets in spring with State Medical Society, and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. Robert H. Akers, 1405 West Broadway, Louisville 3, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. C. P. Naidorf, 411 Parkside Ave. Brooklyn 26, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Robert B. Engle, St. Luke Hospital, Pasadena, Calif. Meets second Wednesday of month in September, November, March, April and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY
Secretary, Dr. Francis J. O'Connor, Augusta General Hospital, Augusta, Maine. Meets in June, September, December and March.

MARYLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

MEMPHIS ROENTGEN SOCIETY
Secretary, Dr. James L. Booth, 899 Madison Ave., Memphis 3, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY
Secretary, Dr. Robert P. Henderson, 316 Medical Arts Bldg., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY
Secretary, Dr. Arthur T. Austin, 104 The Doctors Bldg., Billings, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY
Secretary, Dr. Jerome Zwanger, 126 Hicksville Rd., Massapequa, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. John E. Gary, 1180 Beacon St., Brookline 46, Mass. Meets third Friday of each month, October through May, at The Longwood Towers, Brookline, Mass.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. Harold G. Jacobson, 210th St. and Bainbridge Ave., New York 67, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 4:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville 4, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

OHIO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Francis C. Curtzwiler, 421 Michigan St., Toledo 2, Ohio. Annual meeting: Cincinnati, Ohio, May, 1959.

OKLAHOMA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Edmond H. Kalmon, Jr., 300 Northwest 12th Street, Oklahoma City, Okla. Three regular meetings annually.

OREGON RADIOLOGICAL SOCIETY
Secretary, Dr. C. V. Allen, Veterans Hospital, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. Robert W. Hanf, 900 S. Auburn, Kennewick, Wash. Meets annually in May.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State St., Harrisburg, Pa. Annual meeting: Harrisburg, Pa., April 24–25, 1959.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia 4, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edwin Beck, 3500 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenley Restaurant.

Radiological Section, Baltimore Medical Society
Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Ted F. Leigh, Emory University, Georgia. Annual meeting: New Orleans, La., Nov. 3–6, 1958.

Radiological Society of Greater Cincinnati
Secretary, Dr. Warner Peck, Carew Tower St., Cincinnati 2, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Robert G. Rigler, Straub Clinic, 1020 Kapiolani St., Honolulu 14, Hawaii. Meets third Monday of each month alternately at 4:30 P.M. and 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. Samuel B. Chapman, Jr., 830 Argyle Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. Andrew P. Dedick, Jr., 67 E. Front St., Red Bank, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting: To be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Harold P. Tompkins, 658 S. Westlake, Los Angeles 57, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. John W. Colgan, 277 Alexander St., Rochester 18, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: To be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Irma Smith, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Ralph J. Littwin, Bristol Hospital, Bristol, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Charles E. Bickham, Jr., 1835 Eye St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

Society of Nuclear Medicine
Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. Annual meeting: To be announced.

South Bay Radiological Society
Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. Wayne Reeser, 804 Burroughs St., Conway, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. J. E. Miller, 3500 Gaston Ave., Dallas 10, Texas. Next meeting January 30 and 31, 1959, Statler-Hilton Hotel, Dallas, Texas.

Tri-State Radiological Society
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. Frank A. Kearney, II, 110 S. Curry St., Phoebus, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Wayne A. Chesledon, 306 Stimson Bldg., Seattle 1, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Arnold Myron Wald, 406 Boston Post Road, Port Chester, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Farrell F. Golden, 5221 Tonyawatha Trail, Madison 4, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá
Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá, *Secretary-General*, Dr. Roberto Calderón, Calle Central Deste No. 218, Managua, Nicaragua. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. Guillermo Santín. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 86, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Honorary Secretary, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
Honorary Secretary, Dr. Guillaume Gill, *Associate Honorary Secretary*, Dr. Robert G. Fraser, 1555 Summerhill Ave., Montreal 25, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Louis Ivan Vallée, 1058 rue St. Denis, Montreal 18, Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. Arthur B. Sullivan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

O Colégio Brasileiro de Radiologia
Secretary-General, Dr. Walter Bomfins Pontes. Seat: Rua Major Quedinho, 99-2°. Andar, São Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central, Buenos Aires
Secretary, Dr. Juan L. O. Ambrogna, Montevideo 745, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiologia
Secretary, Dr. Armando Doberti, Merced 565, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejia Dzg., Carrera 13, No. 25-31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuadoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos G., Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ricardo Parada, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Sebastian Nuñez Mier y Téran, Apartado No. 9362, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France. National Meeting Oct. 15–17, 1958 in Paris.

Ceskoslovensk společnost pro Rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha xii, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: To be announced.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgengesellschaft (Société Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the January issue of the Journal.

ANNUAL SYMPOSIUM ON CINEFLUOROGRAPHY

School of Medicine and Dentistry, University of Rochester
Strong Memorial and Rochester Municipal Hospitals
Rochester, New York

Friday, November 14, 1958

4:45–9:30 A.M. Registration

Morning Session: (9:30 A.M. to 12:00 M.)

Speakers	*Title*
George H. Ramsey, M.D. Prof. and Chairman Dept. of Radiology and James S. Watson, Jr., M.D. Research Prof. in Radiology	Purpose of the Symposium
Donald G. Anderson, M.D. Dean, School of Medicine and Dentistry University of Rochester	Welcome
Moderator: Raymond Gramiak, M.D. Instructor in Radiology University of Rochester	
Theodore A. Tristan, M.D. Senior Instructor in Radiology University of Rochester	Methods of Cinefluorography
Mr. A. Lignon North American Phillips Co., Inc.	Image Amplification
Discussion	
J. Feddema, M.D. N. V. Philips' Gloeilampenfabrieken Eindhoven, Netherlands	A 9 Inch Image Tube
Discussion	
Dr. John M. Jacobs General Electric Company	Television Applied to Cinefluorography
Discussion	

Afternoon Session: (1:30 P.M. to 5:00 P.M.)

Moderator: Lee B. Lusted, M.D. Assistant Professor of Radiology University of Rochester	
Speaker	
Mr. Fred Euler Westinghouse Electric Corp.	Synchronization
Discussion	
Dr. Rudolf Kingslake Eastman Kodak Co.	Recording Equipment Lenses
Fred M. O'Brien, Jr. Eastman Kodak Co.	Recording Equipment Cameras
Discussion	
Mr. George M. Corney Eastman Kodak Co.	Cinefluorographic Film
Discussion	

Speakers	*Title*
James S. Watson, Jr., M.D. Research Prof. in Radiology and Mr. Sydney Weinberg Research Associate in Cinefluorography Univ. of Rochester School of Medicine and Dentistry Presented by Mr. Weinberg	Exposure, Processing, and Evaluation of Film Intensifier Combinations
Discussion	

7:15 P.M. Dinner, Sheraton Hotel Speaker: George H. Ramsey, M.D.

Saturday, November 15, 1958

Morning Session: (9:30 A.M. to 12:00 M.)

Moderator: John A. Campbell, M.D.
Professor of Radiology
University of Indiana
Indianapolis, Indiana

Mr. Raymond Quick Assistant Professor of Radiology University of Rochester	Radiation Dose in Cinefluorography A. Physical Measurements
Theodore A. Tristan, M.D. Senior Instructor in Radiology University of Rochester	Radiation Dose in Cinefluorography B. Clinical Practice and Implications
Discussion	
Mr. Gordon A. Chambers Motion Picture Film Dept. Eastman Kodak Co.	Printing and Duplicating Methods
Discussion	
Mr. Frank Dreisinger Picker X-Ray Corp.	Projector and Analytic Equipment
Discussion	
Frank L. Campeti, M.D. Assistant Professor of Radiology University of Rochester School of Medicine and Dentistry	Diagnostic Analysis of Cinefluorographic Film
Discussion	

Afternoon Session: (1:30 P.M. to 5:00 P.M.)

Moderator: Herbert M. Stauffer, M.D.
Professor of Radiology
Temple University School of Medicine and Hospital
Philadelphia, Pennsylvania

Technical Developments Applicable to Cinefluorography

Mr. B. Kazan Hughes Research Lab. Culver City, California	Solid State Amplifying Screen
Discussion	

Speakers	*Title*
Herbert Abrams, M.D. Assoc. Professor of Radiology Stanford University School of Medicine	Biplane, 11-inch Image Intensified Cinefluorography
Discussion	
Dr. Bouwers Old Delft Optical Co. Corp. Presented by Mr. H. P. Bryers	Electro-Optical 12-Inch Image Intensifier
Discussion	
Dr. Jack Ball Picker X-Ray Corp.	Eight Inch Image Intensifier
Discussion	
Herbert M. Stauffer, M.D. Temple University	Polaroid Cinefluorography
Dr. Robert E. Hopkins Professor of Optics University of Rochester	Fiber Optics
Discussion	
George H. Ramsey, M.D.	Summary of the Symposium Program

Group discussions in each field; question and answer period; viewing of equipment.
Symposium registration will be limited to 200. Registration blanks may be obtained by writing to:

George H. Ramsey, M.D.
Department of Radiology
Strong Memorial Hospital
Rochester 20, New York

COURSE IN MEDICAL USES OF RADIOACTIVE ISOTOPES

A four months' course in the Medical Uses of Radioactive Isotopes will be offered at the Queens Hospital Center by the Radiation Medicine Department in cooperation with the Atomic Energy Commission. Course will commence on Tuesday, February 10, 1959, and will consist of weekly five-hour sessions covering lectures, laboratory exercises, and clinical management of patients. The enrollment will be limited. The tuition is $250.00 per person. For information apply to: Dr. Philip J. Kahan, Supervising Medical Superintendent, Queens Hospital Center, 82–68 164th Street, Jamaica 32, New York.

AWARDS IN RADIOLOGICAL RESEARCH JAMES PICKER FOUNDATION

On behalf of the James Picker Foundation, The National Academy of Sciences—National Research Council announces the continued availability of funds in support of radiological research. Applications are reviewed by the Committee on Radiology of the Academy-Research Council's Division of Medical Sciences. Final determination of awards is made by the Foundation upon recommendation of the Division.

In line with the interests of the Foundation, the program is oriented toward, but not necessarily limited to, the diagnostic aspects of radiology. Support is not restricted to citizens of the United States or to laboratories within this country.

Three specific types of support are offered:

(1) *Grants-in-aid* are designed to encourage investigations offering promise of improvement in radiological methods of diagnosis or treatment of disease. Research grants are awarded to institutions, rather than to individuals.

(2) *Grants for Scholars* are a transitional form of support, designed to bridge the gap between the completion of fellowship training and the period when the young scientist has thoroughly demonstrated his competence as an independent investigator. The application is submitted by the institution on behalf of the prospective Scholar. If the request is approved, a grant of $6,000 per year will be made directly to the institution as a contribution toward the Scholar's support, or his research, or both. Initial grants are limited to one year, but renewal for two additional years may be recommended.

(3) *Fellowships in Radiological Research* are open to candidates seeking to gain research skills leading

to investigative careers in the field of radiology. While persons from closely related disciplines are eligible to apply, candidates whose training has been directly in the field of radiology will receive preferences under this program. Candidates must hold the M.D., Ph.D., or Sc.D. degree or the equivalent. Preference will be given to applicants who are thirty-five years of age or less.

Applications in these three categories for the fiscal year 1959–1960 should be submitted by December 1, 1958. Further details and application blanks may be obtained from the *Division of Medical Sciences—Room 411. National Academy of Sciences—National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.*

The National Research Council of Canada has assumed the responsibility for serving as scientific adviser to the James Picker Foundation with respect to its Canadian program. Applications for support of studies to be carried out in Canada should therefore be directed to the Awards Office, National Research Council of Canada, Ottawa 2, Canada.

We regret to announce the sudden death on October 4, 1958 of Dr. Harry M. Weber, distinguished member and past president of the American Roentgen Ray Society.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

RADIOTERAPIA MODERNA. By Prof. Félix Wachsmann, Prof. Gunther Barth, and Dr. Sabino Di Rienzo. Cloth. Pp. 313, with 129 illustrations. Editorial Assandri, Dean Funes 61, Córdoba, Republica Argentina, 1957.

This is a Spanish edition of works by the senior authors especially arranged and translated from the German by their junior collaborator. The book is divided into twelve chapters which deal with: physical principles, biologic foundations, contact therapy, grid therapy, moving (concentration, pendular, rotation) therapy, radioactive isotopes, etc. There is a profusion of graphic curves illustrating absorption, half-value layers, dosimetry, and other physical aspects; and there are numerous photographs of equipment.

Although the avowed aim of this small book is to present recent developments, it devotes considerable space to contact therapy. This form of roentgen therapy is advocated in the treatment of malignant melanomas, claiming 50 per cent cures when no metastases are present; contact therapy is also used for the treatment of carcinoma of the larynx and rectum. No statistical compilations of the results are presented. Overemphasis is equally found on all kinds of moving roentgen therapy techniques which are considered to be indicated for the treatment of tumors of the maxillary sinuses, bronchus, pancreas, large bowel, etc. Roentgen castration of testes is advocated for the treatment of carcinoma of the prostate. Contrasting with outdated biologic generalizations and the lack of consideration of pathology and clinical factors, details of dosimetry are frequently given.

One must agree with the junior author that there is need for a good guide for practitioners of radiation therapy, and not only in the Spanish language. But one must also admit that the young radiologists in search of guidance will receive unbalanced and biased information from the generalizations in this book.

J. A. DEL REGATO, M.D.

THE MEDICAL MANAGEMENT OF CANCER. By Henry D. Diamond, M.D., F.A.C.P., Associate Attending Physician, The Medical Neoplasia Service of the Department of Medicine, The Memorial Center for Cancer and Allied Diseases; Associate, and Section Head of the Lymphoma Section of the Division of Clinical Chemotherapy, The Sloan-Kettering Institute for Cancer Research; Assistant Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y. Cloth. Price, $6.75. Pp. 179, with 40 illustrations and 23 tables. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, 1958.

In this compact monograph the author has compressed into readily usable form most of the available practical information about cancer. There are nine chapters, each discussing the etiology and incidence, pathology and natural history, diagnosis and pathologic physiology, treatment and end results of a separate disease. The first three chapters cover the malignant lymphomas, the leukemias and plasma cell myeloma, all cancers in which the primary treatment is considered to be medical. The last six chapters deal with malignancies in which the primary treatment is surgical, consisting of neuroblastoma, cancer of the lung, thyroid, ovary, breast and prostate. Finally, the appendix contains a discussion of the intracavitary injection of isotopes and a description of radioactive gold, phosphorus and yttrium.

The problems presented by these diseases are on every practicing physician's doorstep. Whether he undertakes treatment himself or guides the patient, he will find much valuable help in this excellent little volume.

WILLIAM S. REVENO, M.D.

ANNUAL REVIEW OF MEDICINE. Volume 9. 1958. David A. Rytand, Editor. Cloth. Price, $7.00. Pp. 530, with illustrations and tables. Annual Reviews, Inc., Stanford, California, 1958.

The ninth volume of this review is again an excellent survey of selected subjects in general medicine. It is of interest to note that the editors have seen fit to include a section entitled "Soviet Medical Research: Some Recent Ad-

vances and Future Plans." Two chapters might be of special interest to radiologists—"Diagnostic Radiology" and "Toxicology of Radioactive Materials."

Some of the subjects are discussed from the medical and surgical standpoint by separate authors. Whereas this leads to some duplication, it does give slightly different viewpoints on these subjects.

The section on hemostatic disorders has much to recommend it. The authors have surveyed the literature but have also been able to inject some of their own thinking. In contrast to this, some of the chapters amount to little more than an annotated bibliography on the given subject. Although the selected bibliography is of value, more comment by the authors would have been appreciated at some points.

This volume is recommended to all physicians for its subject matter and for its extensive bibliography.

Ronald C. Bishop, M.D.

BOOKS RECEIVED

Clinical Radiology of Acute Abdominal Disorders. By Bernard S. Epstein, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, New York; Associate Clinical Professor of Radiology, Albert Einstein College of Medicine, Yeshiva University, New York, New York. Cloth. Price, $15.00. Pp. 352, with 224 illustrations. Lea & Febiger, Washington Square, Philadelphia 6, Pennsylvania, 1958.

Speech Recovery after Total Laryngectomy. By C. J. Hodson, F.R.C.P., D.M.R.E., F.F.R., Deputy Director of the Diagnostic Radiology Department, University College Hospital; and M. V. O. Oswald, F.C.S.T., Late Chief Speech Therapy, University College Hospital, London, and Late Speech Therapist in Charge, St. Pancras Hospital. Paper. Price, $1.50. Pp. 36, with illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, Exclusive U. S. Agents, 1958.

The Cervical Syndrome. By Ruth Jackson, B.A., M.D., F.A.C.S., Clinical Assistant Professor of Orthopaedic Surgery, The University of Texas, Southwestern Medical School, Dallas; Attending Orthopaedic Surgeon, Baylor University Hospital. Second edition. Cloth. Price, $6.50. Pp. 197, with 90 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1958.

A Synopsis of Surgical Anatomy. By Alexander Lee McGregor, M.Ch.(Edin.), F.R.C.S.(Eng.). Consulting Surgeon, Johannesburg General Hospital; Honorary Research Associate, University of the Witwatersrand. Eighth edition. Cloth. Price, $7.00. Pp. 808, with 766 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, 1957.

Fortschritte der Kiefer- und Gesichts-Chirurgie; Ein Jahrbuch. Volume IV. By Prof. Dr. Karl Schuchardt, Direktor der Klinik und Poliklinik für Zahn-, Mund- und Kieferkrankheiten der Universität Hamburg und der Nordwestdeutschen Kieferklinik. Cloth. Price, DM 124.—. Pp. 441, with 314 illustrations and 20 tables. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1958.

A Text-Book of X-Ray Diagnosis by British Authors in Four Volumes. Volume III. Edited by S. Cochrane Shanks, C.B.E., M.D., F.R.C.P., F.F.R., and Peter Kerley, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., D.M.R.E. Third edition. Cloth. Price, $23. Pp. 883, with 802 illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1958.

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides. By G. M. Shy, M.D., M.R.C.P., R. B. Bradley, B.S., and W. B. Matthews, Jr., B.S. From the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service and Department of Health Education and Welfare, Bethesda, Maryland; with a Chapter on Scintillation Spectrometry by J. E. Francis, B.S., P. R. Bell, Ph.D., and C. C. Harris, M.S., Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee. Cloth. Price, $7.00. Pp. 144, with numerous illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, 1958.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. LEUCUTIA, M.D., Harper Hospital, Detroit 1, Michigan

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

HEAD

WEICKMANN, F.: Vicarious hyperplasia of the paranasal sinuses in hypoplastic cerebral processes 881

CEBALLOS, JORGE L., and RENTSCHLER, E. H.: Roentgen diagnosis of sex based on adult skull characteristics; comparison study of cephalometry of male and female skull films (frontal projection) 881

LEGRÉ, J.: Congenital malformations and fracture-subluxations of the craniocervical joint 881

BULL, J. W. D.: Radiological investigation in cases of cerebrovascular disease 881

MALIS, L. I.: The myelographic examination of the foramen magnum 882

NECK AND CHEST

KREPLER, P.: The diagnostic importance of the chest roentgenogram in caudal-cranial position, especially in staphylococcic pneumonia of infants 882

SCHULTZE, G.: Chest film findings in neonatal respiratory distress 883

GEFFERTH, K.: Roentgen changes in moniliasis of the lungs in infancy 883

DAVIS, L. A.: Roentgen manifestations of pulmonary tuberculosis under drug therapy 883

SIANG, SEAH CHENG: Acute (non-specific) lung abscess 883

MCKUSICK, V. A., and FISHER, A. M.: Congenital cystic disease of the lung with progressive pulmonary fibrosis and carcinomatosis 884

SCHOENIGER, E. L., TUCKER, A. S., and BOLANDE, R. P.: Idiopathic pulmonary hemorrhage with hemosiderosis and microcytic anemia 884

HERLITZKA, A. J., and GALE, J. W.: Tumors and cysts of the mediastinum; survey of one hundred seventy-four mediastinal tumors treated surgically during the past eighteen years at the University of Wisconsin Hospitals 884

CODINGTON, J. B., and COWLEY, R. A.: Complete intrathoracic goiter simulating an aneurysm of the ascending aorta; report of a case 885

SCHNEIDERMAN, L. J.: Isolated congenital absence of the right pulmonary artery: A caution as to its diagnosis and a proposal for its embryogenesis—report of a case with review 885

LONGIN, F., and PEPPMEIER, G.: Contribution to the drainage of anomalous pulmonary veins into the vena cava inferior; case report and review of the literature 886

BINDELGLASS, I. L., and TRUBOWITZ, S.: Pulmonary vein obstruction: An uncommon sequel to chronic fibrous mediastinitis 886

BARTHEL, H.: Combination of a right-sided patent ductus Botalli and mitral stenosis 886

GILMAN, R. A., LEHMAN, J. S., MUSSER, B. G., and RUSSELL, R.: Mitral insufficiency—its quantitation by cardiac ventriculography 887

DE VERNEJOUL, R., POINSO, R., JOUVE, A., HENRY, E., SARLES, H., AUBERT, L., LAVAURS, G., and MATTEI, A.: Hydatid cysts of the heart (report of 2 cases) 887

ACKERMAN, J. L., and ALDEN, J. W.: Pneumopericardium following sternal bone marrow aspiration; a case report 888

DEGINDER, W. L.: Pleuroesophageal line in normal chest roentgenograms 888

SOM, M. L., SHAPIRO, J. H., and JACOBSON, H. G.: The "gastric-lined" esophagus with esophagitis 888

RUBINSTEIN, B. M., PASTRANA, T., and JACOBSON, H. G.: Tuberculosis of the esophagus 889

ABDOMEN

SIELAFF, H.-J.: The kymo cassette in the diagnosis of gastrointestinal function 889

AMPLATZ, K.: A new and simple approach to air-contrast studies of the stomach and duodenum 890

MCGEE, ANDREW R., and LOBB, R.: Trichobezoar; with a case report 890

ASCHERMAN, S. W., BEDNARZ, W. W., and OLIX, M. L.: Gastric volvulus; special reference to hepatodiaphragmatic interposition of colon 890

MURPHY, E. S., and YASUDA, A.: Carcinoma of the stomach in Hiroshima, Japan 890

Cooke, L., and Hutton, C. F.: Postbulbar duodenal ulceration 891
Hilbish, T. F., and Black, R. L.: X-ray manifestations of peptic ulceration during corticosteroid therapy of rheumatoid arthritis.. 891
Lowman, R. M., and Davis, L.: The role of water soluble contrast media in gastrointestinal tract obstruction 891
Pearson, S. C., and MacKenzie, R. J.: Intestinal obstruction due to bishydroxycoumarin poisoning 892
Schapira, A., Leichtling, J. J., Wolf, B. S., Marshak, R. H., and Janowitz, H. D.: Diverticulitis of the cecum and right colon: Clinical and radiographic features; report of 18 cases 892
Wigh, R., and Tapley, N. duV.: Metastatic lesions to the large intestine 892
Mussio-Fournier, J.-C., Cervino, J.-M., Ravera, J.-J., Lorenzo y Losada, H., Maggiolo, J., Etcheverrigaray, D., Pereyra, E., and Vanrell, R.: Hypotonia of the colon in four cases of myxedema in adults; its improvement with the use of desiccated thyroid 893
Gershon-Cohen, J., and Fisher, J. F.: Contrast enhancement with television technics: Gallbladder lesions 893
Eelkema, H. H., Starr, G. F., and Good, C. A.: Partial duplication of the gallbladder, diverticulum type; report of a case 893
Ansay, J.: Considerations on 1,000 cholecystographies with volumetric study and curves of gallbladder contractions 893

Gynecology and Obstetrics

Cope, I., and Murdoch, J. D.: The estimation of foetal maturity 894
Poidevin, L. O. S., and Bockner, V. Y.: A hysterographic study of uteri after caesarean section 894
Ferreira, H. P., and Clayton, S. G.: Three cases of malignant change in endometriosis, including two cases arising in the rectovaginal septum 894
Brown, G. R.: Acute hydramnios treated by abdominal paracentesis; case report 895

Genitourinary System

Strandness, D. E., Jr.: The unilateral nonfunctioning kidney 895
Barquín, F., Blanco, P. L., Senra, J., and Barquín, O.: Renal hypertension caused by ossification of the right renal artery 895
Tatelman, M., and Pakusch, R. S.: A comparative evaluation of the newer contrast media for excretory urography 896
Garfinkel, B., and Furst, N. J.: Simultaneous roentgen examination of the urinary and biliary tracts with duografin 896

Skeletal System

Haraldsson, S.: The intra-osseous vasculature of the distal end of the humerus with special reference to capitulum; (preliminary communication) 896
Kerin, R.: Metastatic tumors of the hand... 897
Korttila, K., and Meurman, L.: Eosinophilic granuloma of bone; report of two cases with vertebra plana 897
Gee, V. R., and Pugh, D. G.: Giant-cell tumor of bone 897
Deibert, K. R.: Lytic lesions of ribs 898
LaFond, E. M.: An analysis of adult skeletal tuberculosis 898
Oberniedermayr, A.: Epiphyseal diseases in childhood 899
Ackerman, L. V.: Extra-osseous localized nonneoplastic bone and cartilage formation (so-called myositis ossificans) 899
Schraer, H.: Variation in the roentgenographic density of the os calcis and phalanx with sex and age 899
Bernstein, C., Loeser, W. D., and Manning, L. E.: Erosive rib lesions in paralytic poliomyelitis 900
Gougleris, K., Swoboda, W., and Wolf, H. G.: Involvement of the vertebral column by leukemia in children 900
Henrichsen, E.: Bone formation and calcification in cartilage 900
Steffensen, J. C. A., and Evensen, A.: Bursitis retrocalcanea achillis 900

Blood and Lymph System

McAfee, J. G.: Complications of abdominal aortography 901
Koszewski, B. J., Reedy, W. J., and Iwerson, F.: Sudden death due to translumbar aortography 902
Joos, H. A., and Johnson, J. L.: Retrograde aortography under hypothermia in infancy and early childhood 902
Beebe, R. T., Powers, S. R., Jr., and Ginouves, E.: The early diagnosis of ruptured abdominal aneurysm 902
Husni, E. A.: A new needle and safer method of arteriography 902

General

Blakemore, W. S., Murphy, J. J., Pendergrass, H. P., and Greening, R. R.: Carbon dioxide as contrast medium in roentgenography 903
Pettinari, V., Baccaglini, M., and Castiglioni, G. C.: Opacification of pathologic formations deprived of natural contrast 903
Gould, D. M., and Daves, M. L.: A review of roentgen findings in systemic lupus erythematosus (SLE) 903

Riebel, F. A.: Use of the eyes in x-ray diagnosis 904
Shapiro, J. H., and Jacobson, H. G.: File room operation in a radiology department .. 904

RADIATION THERAPY

Gauwerky, F.: Experiences in the intracavitary therapy of gynecologic carcinoma with cesium 137 904
Brandt, H.-J., and Schlungbaum, W.: Endobronchial irradiation of bronchial carcinoma. 904
Garland, L. H.: The treatment of cancer of the breast. The Carman lecture 905
Dargent, M., Papillon, J., Montbaron, J. F., and Costaz, R.: Urographic study of cancer of the uterine cervix treated by an association of radium and lymphadenectomy. 905
Gray, M. J., Plentl, A. A., and Taylor, H. C., Jr.: The lymphocyst: a complication of pelvic lymph node dissections 906
Baily, N. A., and Beyer, N. S.: Exit dosage for 2-MVP x-rays 906
Pilheu, F. R.: Branchiogenic cysts; a report of 30 cases 907

RADIOISOTOPES

Rosenberg, G.: Biologic half-life of I^{131} in the thyroid of healthy males 907
Schultz, A. L., and Zieve, L.: Relationships between clinical severity of hyperthyroidism and results of thyroid function tests 907
Bolinger, R. E., and Grady, H. J.: The plasma insulin—I^{131} in diabetic patients 908
Seal, S. H., Crosignani, S., Valvassori, G., Nickson, J. J., and Agostino, D.: The treatment of malignant effusions with radioactive colloidal gold (Au^{198}); a review of sixty-six cases 908
Kelly, W. A., Evans, J. P., Harper, P. V., and Humphreys, E. M.: The effect upon hypophysis of radioactive yttrium 909
Fergusson, J. D.: Implantation of radioactive material into the pituitary for the control of prostatic cancer 909
Braestrup, C. B., and Mooney, R. T.: Cobalt-60 radiation measurements 909

MISCELLANEOUS

Soule, A. B., Jr., Heilbronn, H., and Bannister, R.: The rational use of x-ray in medicine and dentistry with particular regard to protective measures 910
Richards, A. G.: Secondary radiation and the dentist 910
Looney, W. B.: Effects of radium in man 911
Porter, K. A., and Murray, J. E.: Long-term study of x-irradiated rabbits with bone-marrow homotransplants 911
Brecher, G., Cronkite, E. P., Conard, R. A., and Smith, W. W. Gastric lesions in experimental animals following single exposures to ionizing radiations 912
Bradshaw, R. L., and Setter, L. R.: Radioactive particles in the atmosphere at Cincinnati, Ohio 912

ROENTGEN DIAGNOSIS

Head

Weickmann, F. Vikariierende Nebenhöhlenhyperplasie bei hypoplastischen Grosshirnprozessen. (Vicarious hyperplasia of the paranasal sinuses in hypoplastic cerebral processes.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1958, *88*, 432–439. (Address: F. Weickmann, Neurochirurg. Klinik, Karower Str. 11, Berlin-Buch, Germany.)

According to Davidoff and Epstein, "The size and shape of the skull usually depends on the degree of development of the brain. Unilateral vicarious hyperplasia of the paranasal sinuses is so constantly associated with cerebral hemiatrophy that the latter diagnosis can be made without encephalography."

The author studied 14 patients with cerebral disease and found hyperplasia of the sinuses in 11 cases. The other 3 patients were as yet too young to manifest these changes in the sinuses. Among the 14 patients were 6 examples of hemiparesis; 6 had mild neurologic disturbances; 7 had psychic disorders; and 3 presented a Sturge-Weber syndrome.

Two patients with advanced bilateral hydrocephalus showed no asymmetry in the skull. The 3 young patients showed only slight asymmetry. In the other 9 cases, the following asymmetries were found: (a) Supra-orbital recessus, 8; (b) homolateral, extensive pneumatization of the frontal sinuses, petrous bone, and lesser sphenoid wings, 4; (c) asymmetry of the vault of the skull, 8; (d) obliquity of the crista galli, 7; (e) obliquity of planum sphenoidale and lesser wings, 7; (f) homolateral thickening of the skull, 5; (g) homolateral loss of relief of inner table, 5; and (h) homolateral elevation of the petrous bone, 4.

In the presence of convulsions, asymmetry of the skull and sinuses indicates that the cerebral damage occurred in early childhood and unilateral hyperplasia of the sinuses indicates homolateral cerebral atrophy.—*J. Zausner, M.D.*

Ceballos, Jorge L., and Rentschler, E. H. Roentgen diagnosis of sex based on adult skull characteristics; comparison study of cephalometry of male and female skull films (frontal projection). *Radiology*, Jan., 1958, *70*, 55–61. (Address: E. H. Rentschler, University of Texas Medical Branch, Galveston, Texas.)

The authors report the results of a study comparing skull roentgenograms of the male and female adult. Comparison of 100 normal adult male and 100 normal adult female skulls was made from a roentgenologic standpoint. They were compared as to sagittal diameter, mastoid length, mandibular width at the level of the mastoid tips, and mandibular angle width.

The comparison of the findings in these two groups shows that there are characteristic dimensions for the male and female and that sex can be predicted in 88 per cent of the cases by utilization of the dimensions.—*Walter H. Jarvis, Jr., M.D.*

Legré, J. Les malformations congénitales et les fractures-luxations de la charnière craniocervicale. (Congenital malformations and fracture-subluxations of the craniocervical joint.) *J. de radiol., d'électrol. et de méd. nucléaire*, March–April, 1958, *39*, 124–133. (From: Service Central de Radiologie et Clinique Neurochirurgicale, Hôpital de la Timonte, Marseille, France.)

The author has collected over a period of one year a number of congenital and acquired malformations of the craniocervical joint. A few of these conditions are illustrated and briefly discussed. They are divided as follows: *Minor Abnormalities:* (1) Fusion by congenital dysostosis of one or more cervical vertebrae, chiefly the epistropheus and C_3; (2) spina bifida of the atlas due to the dehiscence of its posterior arch; and (3) abnormalities of the foramen magnum (stenosis, asymmetry, widening), interesting chiefly when associated with the Arnold Chiari syndrome. *Major Abnormalities:* (1) Basilar impression (primary or secondary); (2) occipitalization of the atlas (complete or partial); and (3) post-traumatic atlaido-epistropheal dislocations.

According to the author's experience, standard roentgenograms of the skull and cervical spine must be complemented with sagittal and lateral laminagrams to correctly diagnose these conditions.—*H. P. Lévesque, M.D.*

Bull, James W. D. Radiological investigation in cases of cerebrovascular disease. *Brit. M. J.*, April 5, 1958, *1*, 795–797. (From: St. George's Hospital, and National Hospital for Nervous Diseases, London, England.)

Ten years' experience with cerebral angiography in the investigation of cerebrovascular lesions has indicated the uncertainties of clinical diagnosis. Previous to this last decade, during which radiology has played a part in the investigation, the diagnosis of the more common cerebrovascular lesions was represented to the student as being fairly straightforward. Because not many cases of "stroke" were seen in the wards of a teaching hospital, and only a minority of those were examined at necropsy, there was little opportunity of confirming or refuting diagnoses.

The roentgenologic examinations of the skull include plain roentgenograms, angiography and pneumoencephalography.

Plain roentgenograms should be obtained routinely. Angiography has improved diagnosis and thus renders the treatment of "stroke" more rational. In addition, retrospective analysis has sharpened our ability to make a correct diagnosis clinically. Angioma and internal carotid thrombosis are 2 examples of this fact. Ten years ago doctors in the neurologic field seldom mentioned either condition in differential diagnosis, while today both are frequently considered. The indications for angiography are discussed in some detail; including subarachnoid hemorrhage, hemorrhage, thrombosis, embolism, tumor, and subdural hematoma. Although there is a tendency to assume that pneumoencephalography has only a minor place in the investigation of cerebrovascular diseases, it may give a more accurate picture of the size and position of the lesion when carotid angiography shows a major displacement.—*John F. Weigen, M.D.*

Malis, Leonard I. The myelographic examination of the foramen magnum. *Radiology*, Feb., 1958, *70*, 196–221. (Address: The Mount Sinai Hospital, New York 29, N. Y.)

The author describes in detail a technique for myelographic examination of the region of the foramen magnum. The patient is instructed to attempt to hold his head and neck as they are positioned by the examiner, and an attempt is made to instruct him in flexion and extension of the neck as separate functions from flexion and extension of the head. A lumbar puncture and instillation of oil is performed in the usual manner. If a Queckenstedt test demonstrates an open system, an average of 12 cc. of pantopaque is used; if there is a complete block, the amount of oil is reduced 2 or 3 cc. The oil is then brought up into the cervical region, usually by holding the head and neck in hyperextension and tilting the table head down, being careful not to allow the oil to reach a level high enough to enter the foramen magnum as it pours over the dorsal hump. This is facilitated by placing a pillow beneath the patient's hips, thus reducing the degree of tilt and allowing minimal hyperextension of the head. If the routine injection of 12 cc. appears inadequate after entering the cervical canal, a further 6 to 12 cc. is added. The table is then returned to the horizontal position and tilts are thereafter limited to 15° to 20° in either direction, depending upon the manipulative needs, thus obviating the necessity of restraining devices for the remainder of the examination. The use of a lateral fluoroscope or a biplane fluoroscope greatly assists in the examination, but is not necessary, as the ordinary fluoroscopic table with the addition of cross-table lateral roentgenograms taken on a grid cassette can provide the same information.

With the patient in a flat position with the oil in the cervical canal, if the head and neck are flexed together a point will be reached in which the foramen magnum will be sufficiently low to allow oil to run in along the clivus. Since the clivus will be pointed rather sharply downward at this point, the oil will run forward, pour over the posterior clinoids, and disperse in the anterior and middle fossa. If, however, the head is maintained in some extension and the neck is brought forward into flexion, it is possible to lower the foramen magnum below the level at which the oil will run into it and at the same time to keep the angle of the clivus tilted slightly upward from the foramen to the posterior clinoid so that oil entering this region can be maintained in the gutter of the clivus, where it can be controlled, examined, and recovered. With a little experience, one can determine the proper angles of tilt and flexion, and control the oil with reasonable ease with the usual fluoroscope table. Lateral roentgenograms are made after filling of the clivus has been visualized fluoroscopically in the anteroposterior projection and appropriate anteroposterior spot roentgenograms have been taken.

The author presents several cases with roentgenograms and excellent line drawings to illustrate the normal findings and variations as well as the changes due to lesions at the foramen magnum. Any defect seen beneath a fluid level on the cross-table lateral roentgenograms must be significant, and in general the demonstration of such is used as the criterion for the genuineness of the lesion. It is not felt that there is any real danger to the patient if some of the pantopaque enters the cranial cavity. More important is the necessity of exercising extreme caution regarding the manipulations suggested here as they may not be tolerated well by patients with cervical lesions.—*Walter H. Jarvis, Jr., M.D.*

Neck and Chest

Krepler, P. Zur diagnostischen Bedeutung der Röntgenaufnahme des Thorax in kaudokranialer Hängelage, insbesondere bei der Staphylokokkenpneumonie des Säuglings. (The diagnostic importance of the chest roentgenogram in caudal-cranial position, especially in staphylococcic pneumonia of infants.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, March, 1958, *88*, 357–359. (Address: P. Krepler, St.-Anna-Kinderspital, Kinderspitalgasse 6, Wien 9, Austria.)

Staphylococcic infection of the lungs and its complications of empyema and lung abscess often require information from a roentgenologic examination which is difficult to obtain by clinical examination. When it is desirable to differentiate between a lung abscess and an encapsulated pleural empyema, not only a lateral decubitus, but also an upside-down chest roentgenogram with the infant held up by its feet should be made. Such an additional roentgenogram allows very often a definite location of all the

borders of the cavity, even the most inferior one, because of the shift of the air into the uppermost position. The procedure is not difficult and is without danger.—*Hans W. Hefke, M.D.*

Schultze, Gunter. Chest film findings in neonatal respiratory distress. *Radiology*, Feb., 1958, *70*, 230–237. (Address: 601 N. Broadway, Baltimore 5, Md.)

The author presents a correlation of clinical, pathologic, and roentgenographic chest findings in 100 infants with respiratory distress during the neonatal period.

Bilateral, diffuse, coarse, irregular densities in the lungs were present in 20 premature and full-term infants. Ten of these exhibited immediate postnatal respiratory distress, and 10 did not demonstrate such findings until after the lapse of some time. Seven were premature and 13 were full-term infants. Three deaths occurred in this group. Bilateral, coarse, irregular densities appear to be associated with bronchopneumonic processes.

Fine, diffuse, reticular opacifications usually involving both lungs simultaneously were shown on roentgenograms of 20 infants. Eighteen of the 20 infants were premature. Ten of the infants in this group had respiratory distress immediately following birth. There were 8 deaths in this group. The essential pathologic findings in one-third of the infants showing the reticuloglandular pattern was diffuse hyaline membrane disease with secondary atelectasis in varying degree. In the large majority of infants less than six days old, the reticuloglandular pattern is probably associated with hyaline membrane disease.

Miscellaneous patterns, including lobar infiltrations, pneumothorax, rounded radiolucent lesions and changes suggesting massive atelectasis were found in 13 infants. In 47 infants the chest roentgenograms showed no significant abnormalities in spite of respiratory distress. Several reasons for this are discussed.—*Arno W. Sommer, M.D.*

Gefferth, K. Über Röntgenveränderungen bei Lungenmoniliasis im Säuglingsalter. (Roentgen changes in moniliasis of the lungs in infancy.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, March, 1958, *88*, 347–356. (Address: Bókay J. u. 53, Budapest, Hungary.)

Generalized moniliasis with involvement of the lungs has become a more frequent disease since the introduction of antibiotics. The author describes 5 cases of moniliasis of the lungs. Of these 5, only one infant died; the other 4 recovered. In most cases the infection was superimposed on other infectious diseases.

The roentgen findings were most often hilar enlargement and perihilar soft, sometimes fine, nodular densities. The chronicity of these findings rules out an acute bronchopneumonia. Atelectatic areas can occur as well as emphysematous blebs. The fine nodular shadows represent small granulomas of the lung. Occasionally the nodulation may simulate the coarser nodules of miliary tuberculosis.—*Hans W. Hefke, M.D.*

Davis, Lawrence A. Roentgen manifestations of pulmonary tuberculosis under drug therapy. *Radiology*, Feb., 1958, *70*, 247–251. (Address: 226 E. Chestnut St., Louisville, Ky.)

During the treatment of pulmonary tuberculosis in children, several unusual changes may appear on the chest roentgenograms which cannot be correlated with the clinical picture. Frequently, patients who are considered to be asymptomatic and are obviously improving clinically, will, during some phase in the course of drug therapy, show a large area of segmental infiltration or collapse or several patches of obstructive emphysema, when previously the roentgenograms had demonstrated progressive resolution of the original lesion. Most of these changes will disappear if the original drug treatment is continued and they should be carefully evaluated so that premature surgical intervention will be avoided.

Four representative case histories with the respective chest roentgenograms are presented.—*Z. Petrany, M.D.*

Siang, Seah Cheng. Acute (non-specific) lung abscess. *Proc. Alum. Ass. Malaya*, Dec., 1957, *10*, 267–296. (From: University of Malaya, Singapore.)

This is a comprehensive article concerning 40 cases of nonspecific lung abscess seen from 1952 to 1956.

Thirteen of the 40 cases were found to have clubbing of the fingers. None of these patients had carcinoma of the lung and the fully developed picture of pulmonary osteoarthropathy, which is seen frequently with carcinoma of the lung, was not observed.

The most commonly involved segments were the apical of the lower and the posterior of the upper lobes. The relationship to the often seen gross dental caries and gingival sepsis in this part of the world is pointed out.

The roentgenographic finding of an air fluid cavity is felt to represent only a stage in the disease. Thin-walled annular pulmonary lesions were seen frequently and were thought to represent bullae in the healing area. These lesions were all temporary in nature and eventually resolved completely.

The patients were treated, for the most part, with penicillin only, though some had penicillin followed by aureomycin, terramycin, and chloromycetin, or aureomycin and chloromycetin alone. Two of the cases were treated with streptomycin and penicillin in combination. Part of the therapy consisted of

postural drainage under the guidance of a physiotherapist. This was felt to be extremely valuable in the healing process.

The author feels that the majority of patients can be cured by careful medical management with adequate and, if necessary, prolonged chemotherapy; and that the remaining minority eventually will require surgical treatment to complete the cure.—*Stephen Bruny, M.D.*

McKusick, Victor A., and Fisher, A. Murray. Congenital cystic disease of the lung with progressive pulmonary fibrosis and carcinomatosis. *Ann. Int. Med.*, April, 1958, *48*, 774–790. (From: The Department of Medicine, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Md.)

The authors report 3 male patients who died of progressive pulmonary insufficiency at the ages of thirty-two, forty, and fifty-three years, respectively. Postmortem studies on 2 of the patients revealed numerous small cysts 1 to 2 mm. in diameter, pulmonary fibrosis, and primary carcinoma of the lung. The third individual, a sibling of one of the autopsied patients, died of pulmonary insufficiency after a similar course, but postmortem studies were not done. Clubbing of the fingers had been present for many years prior to the onset of significant respiratory symptoms in all 3 patients. The authors emphasize that this could pass as isolated familial clubbing because of the lack of symptoms and roentgen abnormalities.

Small cysts of the type reported are not visible on roentgenograms. The only roentgenologic sign, until very late in the patient's course, is slight generalized reticulation of the lung fields. Late signs include marked progression of the reticular pattern and increasing prominence of the main pulmonary artery. Bronchograms in this type of cystic disease are rarely positive.

The authors believe that the numerous small cysts are congenital and hereditary, and they feel that both the pulmonary fibrosis and carcinomatous degeneration are complications of true congenital cystic disease.—*John L. Williams, M.D.*

Schoeniger, Ernest L., Tucker, Arthur S., and Bolande, Robert P. Idiopathic pulmonary hemorrhage with hemosiderosis and microcytic anemia. *Radiology*, Feb., 1958, *70*, 191–195. (Address: A. S. Tucker, University Hospitals of Cleveland, 2065 Adelbert Road, Cleveland 6, Ohio.)

Idiopathic pulmonary hemosiderosis is a rare disease which exhibits unusual and characteristic findings in the chest roentgenogram. The authors report in detail such a case in a young girl who was followed from the age of nine years until her death three years later at the age of twelve years. The patient was first seen because of mild hemoptysis following an episode of low-grade fever. Other than a moderate microcytic anemia, all examinations including extensive laboratory studies were normal. A posteroanterior chest roentgenogram revealed diffuse bilateral streaky and mottled fine densities with a tendency to coalescence. After conservative treatment and one unit of whole blood, a repeat chest roentgenogram nineteen days later revealed a marked degree of improvement. Following an asymtomatic interval of nearly three years the patient was again admitted for hemoptysis and fever and again the chest roentgenogram revealed bilateral pulmonary infiltration of the same nature as that found on the original examination, but considerably more extensive. The patient improved with only supportive therapy and again the chest roentgenogram appeared normal. Three months later the patient expired from severe pulmonary hemorrhage. Autopsy findings revealed both lungs to be firm, heavy, and reddish-brown. Microscopic examination disclosed hemosiderin deposition in the hilar lymph nodes and hemosiderin in the alveoli, both free and within alveolar macrophages.

This disease of obscure etiology is most often observed in children and is usually fatal within a few years. The symptomatology is usually the same. Hemoptysis is invariably present and as the disease progresses the patients develop tachypnea, dyspnea, pallor, tachycardia, low fever, slight cyanosis and ultimately jaundice. The iron deficiency anemia is striking. Roentgenographically, the appearance is characteristic with mottled fine densities arranged in a miliary or patchy distribution. Three criteria which have been emphasized are: multiple pulmonary consolidations, which clear in a week or so; changing patterns of coalescence; and an underlying reticulostriate pattern.

The authors emphasize that this diagnosis should be considered in all young patients with hemoptysis who present a diffusely mottled pulmonary infiltration which changes, clears and recurs.—*Edward B. Best, M.D.*

Herlitzka, Alfred J., and Gale, Joseph W. Tumors and cysts of the mediastinum; survey of one hundred seventy-four mediastinal tumors treated surgically during the past eighteen years at the University of Wisconsin Hospitals. *A.M.A. Arch. Surg.*, May, 1958, *76*, 697–706. (Address: A. J. Herlitzka, 1300 University Ave., Madison, Wis.)

This report deals with 174 patients with mediastinal tumors or cysts observed between 1939 and 1957. Ninety-two females and 82 males are represented.

The mediastinum is divided into 2 major compartments, the superior and inferior, being separated by

a line drawn from the angle of Lewis posteriorly to the fourth thoracic vertebral body. The inferior mediastinum is divided into the anterior, hilar and posterior inferior portions.

The occurrence of mediastinal tumors or cysts in this series was as follows: (1) Anterior superior, 20 per cent; (2) anterior inferior, 20 per cent; (3) hilar area, 20 per cent; and (4) posterior inferior, 30 per cent. The 10 per cent remaining were miscellaneous lesions in combined areas.

The diagnosis was made roentgenologically in 68 per cent of the cases. Twenty-five per cent of the entire group were malignant; of these 45 lesions, 20 were resectable.

The types of lesions in order of frequency were as follows: (1) Neurogenic tumors, 20.1 per cent; (2) teratodermoids, 14.9 per cent; (3) bronchogenic cysts, 13.8 per cent; (4) pericardial cysts, 9.8 per cent; (5) thymomas and thymic cysts, 8.0 per cent; (6) lymphomas, 7.0 per cent; (7) intrathoracic goiters, 5.7 per cent; and (8) miscellaneous, 20.7 per cent.

Neuroblastomas in the younger age group and neurofibrosarcomas in the adults were the most frequent and 83 per cent of these lesions occurred in the posterior mediastinum.

Teratodermoids were second in frequency, all being located in the anterior inferior mediastinum. It is felt by the authors that these occur related to the third branchial cleft, the same origin as thymus.

The bronchogenic cysts were usually found in the hilar or posterior mediastinal area, related to the trachea or major bronchi and for the most part in the third and fourth decades of life.

Pericardial cysts were typically located in the anterior inferior mediastinum, lying against the pericardium, diaphragm or chest wall. They were occasionally confused with diaphragmatic hernia, dermoid cysts or pericardial fat pads.

The thymomas and thymic cysts numbered fewer than in other large series reported, being 14 in total number, of which 4 were malignant. They, for the most part, occurred in the anterior superior mediastinum.

Of the 12 lymphomas, 6 were hilar and 5 anterior mediastinal. One had an increased I^{131} uptake and was misdiagnosed as an intrathoracic thyroid.

Nine of the 10 intrathoracic goiters were located in the anterior superior mediastinum. When unilateral, 6 of the 7 were located on the right side. The average age was sixty years and 6 of the 10 occurred in females. Two patients were toxic.

Of the remaining 36 miscellaneous tumors, 18 were malignant.

As noted, 7 out of 10 of these lesions can be diagnosed prior to surgery by roentgenograms, but one must consider cardiovascular abnormalities, diaphragmatic defects or esophageal and pulmonary lesions. Of all the lesions found in this series, three-quarters were benign. Of the 20 resected malignant lesions, 10 had no obvious recurrence two or more years after surgery. The authors feel that surgery is indicated once the mediastinal tumor or cyst is detected.—*Stephen Bruny, M.D.*

Codington, John B., and Cowley, R. Adams. Complete intrathoracic goiter simulating an aneurysm of the ascending aorta; report of a case. *J.A.M.A.*, May 24, 1958, *167*, 461–463. (From: The Department of Surgery, University of Maryland School of Medicine, Baltimore, Md.)

The authors report the case of a thirty-nine year old woman who complained of pain in her chest and back. A routine chest roentgenogram showed a mass on the right, adjacent to the ascending aorta, measuring about 4×5 cm. Fluoroscopic examination suggested that the mass changed in size during the Valsalva maneuver and seemed to pulsate. A retrograde aortogram showed considerable vascularity which gave the impression of an aneurysm arising from the ascending aorta.

Radioactive iodine studies suggested that the mass was thyroid tissue.

Exploration of the neck showed a normal thyroid gland and subsequent thoracotomy showed a nodule 4.5×3.5×3 cm. fixed to the anterior ascending aorta which was shown by microscopic examination to be adenomatous thyroid tissue.

This lesion was unusual in that there was no connection with the thyroid in the neck, and the vascular supply apparently arose directly from the aorta. —*George L. Sackett, Jr., M.D.*

Schneiderman, Lawrence J. Isolated congenital absence of the right pulmonary artery: A caution as to its diagnosis and a proposal for its embryogenesis—report of a case with review. *Am. Heart J.*, May, 1958, *55*, 772–780. (From: The Mallory Institute of Pathology, Boston City Hospital, Boston, Mass.)

Isolated true congenital absence of the pulmonary artery is rare. Only 11 well documented proved cases can be found in the literature at present. Nine of these are of the right side and 2 of the left. The anomaly on the left is usually accompanied by other anomalies, most frequently tetralogy of Fallot. The absence of the right pulmonary artery is usually not associated with other anomalies, except occasionally with patent ductus arteriosus or coarctation of the aorta.

Congenital absence of the pulmonary artery requires an anomalous blood supply to the affected lung. If this cannot be demonstrated, congenital absence of the pulmonary artery should be a questionable diagnosis.

The 4 cardinal signs of congenital absence of the

pulmonary artery are: (1) roentgen demonstration of diminished pulmonary vascular markings; (2) diminished size of the affected hemithorax; (3) mediastinal shift to the affected side; and (4) absent "hilar comma" shadow. The clinical diagnosis is best made by angiocardiography, but the anomalous blood supply to the lung must be demonstrated to rule out occlusion or atresia.

The author discusses the possible embryologic development of this anomaly in detail. It is due to some defect in the development of the sixth aortic arch. The article should be read to best understand the developmental possibilities. The time the defect occurs has been pin-pointed to the time of the division of the truncus or about the thirty-first to the thirty-sixth day.—*Frank M. Windrow, M.D.*

Longin, F., and Peppmeier, G. Beitrag zur anomalen Lungenveneneinmündung in die Vena cava inferior; Mitteilung eines Falles und Literaturübersicht. (Contribution to the drainage of anomalous pulmonary veins into the vena cava inferior; case report and review of the literature.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1958, *88*, 386–400. (From: Medizinische Poliklinik der Universität, Würzburg, Germany.)

Although anomalous pulmonary veins draining into the vena cava have been known to pathologists since 1836, it has remained for Grishman, Poppel *et al.* in 1949 to report the first clinical and roentgenologic observations of this condition.

A single case is reported concerning a female, aged forty-eight, who had suffered from bronchitis and recurrent attacks of pneumonia during childhood. At the age of fourteen an anomalous position of the heart had been noted. There had been dyspnea on exertion at frequent intervals, especially following tonsillectomy at the age of twenty-three. Between the age of twenty-six and thirty there had been 2 normal deliveries and 2 miscarriages. These were followed by attacks of severe hemoptysis. Her chief complaints were precordial pain, dyspnea on slightest exertion, palpitation and angina pectoris.

Physical examination revealed slight cyanosis of the lips and finger tips, diminished breath sounds over the right lower lobe and rales over the right upper lobe. The heart was displaced to the right. There was arrhythmia and a systolic murmur in the right fourth and fifth intercostal spaces, parasternally. The liver was slightly enlarged and the electrocardiogram revealed auricular fibrillation.

Roentgenologic examination disclosed displacement of the heart to the right, bulge of the right pulmonary artery and an atypical vascular shadow in the right middle lung field which widened toward the base. Laminagraphy showed an abnormal dichotomous vascular pattern in the right lung which became wider caudally and converged toward the right base. A cardiac catheter introduced through a saphenous vein led into the right upper lung field. Blood samples taken through the catheter revealed highly oxygenated blood. Therefore, the following diagnoses could be made: (1) anomalous right pulmonary veins draining arterialized blood into the vena cava inferior, (2) dextroposition of the heart, atrial septal defect with right-to-left shunt, (3) hypoplasia of the right pulmonary artery, and (4) hypoplasia of the right lower lobe, large right upper lobe and upward displacement of the right middle lobe, also diminished vital capacity of the right lung.

There is no follow-up report of this interesting and well illustrated case, but the literature, especially of American authors, is reviewed in detail.—*Ernest Kraft, M.D.*

Bindelglass, Irving L., and Trubowitz, Sidney. Pulmonary vein obstruction: An uncommon sequel to chronic fibrous mediastinitis. *Ann. Int. Med.*, April, 1958, *48*, 876–891. (From: The Medical Service, Veterans Administration Hospital, East Orange, N. J.)

The authors report the case of a twenty-five year old Negro who was admitted to the hospital with complaints of recurrent "asthma" and hemoptysis of one month's duration. When he was eight years old, he had been hospitalized for seven weeks for a respiratory illness, which was diagnosed as acute bronchopneumonia. Following this he suffered from mild, nondisabling respiratory distress which persisted and necessitated him being kept on light duty during a two year army service.

On admission he was dyspneic at rest. Roentgenograms of the chest revealed increased pulmonary vascular marking, greatest in the upper lobes. The hilar segments were markedly prominent, but there was no hilar dance. Electrocardiograms showed right axis deviation and cor pulmonale. Episodes of hemoptysis and pulmonary edema occurred from time to time for two months, the final being fatal. This originated during bronchoscopy. Autopsy revealed an extensive, posterior mediastinitis involving primarily the pulmonary veins issuing from the lower lobes. The process appeared to be relatively old, with advancing healing seen in the form of collagenization and ossification. There were no specific pathologic features.

Five other cases of pulmonary vein stenosis due to chronic, fibrous mediastinitis have been found in the literature. This fibrosis characteristically lacks specificity and is probably the end result of different etiologic processes and pathogenetic mechanisms. It is difficult to establish a correct antemo-tem diagnosis.—*Arthur E. Childe, M.D.*

Barthel, Heinz. Kombination eines rechtsseitigen offenen Ductus Botalli mit einer Mitralstenose. (Combination of a right-sided patent ductus Botalli and mitral steno-

sis.) *Thoraxchirurgie*, August, 1957, *5*, 105–110. (Address: H. Barthel, Chirurgische Universitätsklinik, Eppendorf, Hamburg, Germany.)

Although combinations of congenital anomalies and acquired valvular lesions of the heart are not uncommon, the findings of mitral stenosis complicating a patent ductus arteriosus leading from the right pulmonary artery to the right subclavian artery are unheard of clinically.

Such a combination is reported in a thirty-four year old male with the following history: During childhood the patient had frequently suffered from throat infections, but had always been physically fit in spite of a "slight cardiac condition." At the age of twenty he had been hospitalized for three months because of pleurisy and painful swelling of his fingers and wrists. This condition recurred during the following two years and necessitated frequent aspirations of bilateral pleural effusions. These episodes were followed by occasional hemoptysis and dyspnea on exertion. After three more years transient pulmonary edema and slight hemiparesis developed which was believed to be due to mitral disease and cerebral embolism. Because of further progression of the disease the patient was finally referred for cardiac surgery.

Preoperative examinations with cardiac catheterization established the diagnosis of patent ductus arteriosus and mitral stenosis. Roentgenologically, the left atrium caused only slight indentation of the barium-filled esophagus, but the pulmonary trunk showed aneurysmal dilatation and vigorous pulsation. Therefore, it was believed that the hemodynamic changes due to mitral valve lesion were less prominent than the findings of a left-to-right shunt. This impression was confirmed surgically. At operation the right pulmonary artery was found to be anterior to the ascending aorta, somewhat compressed by the latter. The suspected anomalous artery was found to arise from the pulmonary conus and to extend obliquely upward to the right side. It communicated with the right subclavian artery. Ligation of this anomalous patent ductus arteriosus resulted in removal of the arterial shunt and in marked improvement of the patient's condition.

A patent ductus arteriosus on the right side arising from the pulmonary trunk is believed to occur in 2 per cent of all patent duct cases. Embryologically, there is a common origin of the sixth branchial artery and of the pulmonary artery at the right cardiac outflow tract. In this case, however, the origin was separate, and in the further course of embryologic development the sixth branchial artery failed to become obliterated.—*Ernest Kraft, M.D.*

Gilman, Richard A., Lehman, J. Stauffer, Musser, Benjamin G., and Russell, Richard. Mitral insufficiency—its quantitation by cardiac ventriculography. *J.A.M.A.*, April 26, *166*, 2124–2126. (Address: J. S. Lehman, 230 N. Broad St., Philadelphia 2, Pa.)

Anatomic changes in the mitral valve leaflets causing regurgitation may preclude successful surgical treatment. Since the advent of surgical treatment of mitral stenosis, the importance of preoperative assessment of the presence and degree or absence of mitral regurgitation has become evident.

"Cardiac ventriculography" consists of direct transthoracic needle puncture opacification of the ventricles of the heart. This has also been termed "cardioangiography" by others.

The results of cardiac ventriculography are reported for 32 patients who also underwent surgical exploration of the mitral valve. The ventriculographic studies were graded with respect to the presence or absence of regurgitant opacification of the left atrium. Any degree of regurgitant opacification of the left atrium is felt to indicate mitral valve insufficiency.

Considering operative findings at surgical exploration of the mitral valve as indicative of the presence or absence of mitral regurgitation, there were no false positive ventriculographic diagnoses of mitral insufficiency and the procedure appears to provide a fairly accurate method for objective demonstration of the presence of mitral insufficiency.—*John F. Weigen, M.D.*

de Vernejoul, R., Poinso, R., Jouve, A., Henry, E., Sarles, H., Aubert, L., Lavaurs, G., and Mattei, A. (Marseille and Toulon, France.) Les kystes hydatiques du coeur; (à propos de deux observations). (Hydatid cysts of the heart [report of 2 cases].) *Presse méd.*, April 23, 1958, *66*, 697–700.

Although echinococcus disease is relatively infrequent in France, the authors have been able to observe two rare incidents of hydatid cysts in the heart muscle.

The first patient was a male, aged thirty, who for several months had suffered from sharp precordial pain radiating to the neck and the left shoulder with associated insomnia. Cardiac enlargement had already been known to exist at the age of twenty-three. There was no history of echinococcus disease. Roentgen examination revealed cardiac enlargement to the left with a sharp bulge of the left ventricle. Curvilinear calcium densities were also noted within the bulge. Electrocardiograms showed left axis deviation, inverted T-wave and signs of myocardial ischemia. Angiocardiograms disclosed indentation of the right ventricular chamber and marked crowding of the left ventricular chamber. The area of the bulging left cardiac apex failed to become opacified. In view of the abnormal electrocardiogram and the soft tissue mass at the cardiac apex, a tentative diagnosis of a

hydatid cyst of the heart was made. This impression was confirmed surgically. At operation a multilocular cyst was enucleated and the patient made an uneventful recovery.

The second patient was a female, aged thirty-one, suffering from a protracted fever which gradually increased to 104° F. At the age of nineteen hydatid cysts were discovered in the region of the appendix during an appendectomy. Three years later cysts were discovered in the liver and in the parietal peritoneum. After five more years a sudden severe cardiovascular collapse occurred with associated diarrhea and vomitus. Differential blood count revealed an eosinophilia of 17 per cent. Roentgen studies at this time disclosed a left cardiac enlargement, mostly in a downward direction. Angiocardiograms showed a normal dextrogram; but the left ventricular chamber was elevated, decreased in size and encroached upon from below. The electrocardiogram revealed signs of coronary ischemia similar to findings in the first case. At operation an orange-sized multilocular hydatid cyst was removed which resulted in complete relief of symptoms.

Echinococcus disease is prevalent in North Africa, South America, Australia, New Zealand and the Middle East, but rare in France. Cardiac involvement has been reported as high as 13.6 per thousand and as low as 0.7 per thousand cases. The parasite enters the heart muscle through the coronary circulation, the left ventricle being the site of predilection.

Clinically, the so-called silent group is seen most frequently. With electrocardiographic findings of myocardial ischemia in a young person cardiac, hydatid cyst must always be considered a possibility, especially in countries where the disease is prevalent. In a second group there are symptoms of cardiac tumor with signs of palpitation, exertional dyspnea, precordial pain and arrhythmia.

A diagnosis of cardiac localization can easily be assumed when hydatid cysts are found in other parts of the body, when the heart increases in size from year to year and when curvilinear calcifications are found within the heart shadow. Specific angiographic findings and an electrocardiogram which is positive for myocardial ischemia and impaired coronary circulation in a young person tend to support the suspicion of hydatid involvement of the heart.

In this new era of cardiac surgery, complete recovery can be achieved by removal of the multilocular cysts. Therefore, early recognition of the condition is vitally important.—*Ernest Kraft, M.D.*

Ackerman, Joseph L., and Alden, John W. Pneumopericardium following sternal bone marrow aspiration; a case report. *Radiology*, March, 1958, *70*, 408–409. (From: Department of Radiology, The Delaware Hospital, Wilmington, Del.)

In a review of the English literature back to and including 1950, the authors could find no report of pneumopericardium resulting from a routine sternal bone marrow aspiration. They present one such case in which a physician, during sternal puncture, accidentally went too deep. The patient, however, exhibited no reaction, and when marrow was not obtained, the procedure was postponed and considered unsuccessful. The following day roentgen examination of the chest revealed air in the pericardial space. Four days later, air was still demonstrable. Eventually, it disappeared completely.

A series of roentgenograms show the findings.—*Z. Petrany, M.D.*

DeGinder, William L. Pleuroesophageal line in normal chest roentgenograms. *J.A.M.A.*, May 24, 1958, *167*, 437–441. (Address: 2410 Rio Grande, Austin, Texas.)

Most persons retain a small volume of air in the upper thoracic esophagus when in the erect position. At the same time, the heart and vessels are drawn downward resulting in narrowing of the upper mediastinum in its transverse diameter. This traction effect is said to produce a slight negative pressure in the upper esophagus which is usually neutralized by a small amount of air.

In this situation, the posteroanterior roentgenograms show a continuous curved line of soft tissue density extending from the right apex downward across the second or third thoracic vertebrae toward the aorta. Air is present on both sides of the line, which varies from 3 mm. to 8 mm. in width.

If air is not present in the esophagus, only the margin of air-filled right lung against the mediastinum is seen.—*James J. McCort, M.D.*

Som, Max L., Shapiro, Jerome H., and Jacobson, Harold G. The "gastric-lined" esophagus with esophagitis. *Radiology*, Dec., 1957, *69*, 856–859. (Address: M. L. Som, Montefiore Hospital, 210th St. and Bainbridge Ave., New York 67, N.Y.)

The distal end of the esophagus may occasionally be lined by glandular or atrophic gastric mucosa. Allison and Johnstone considered this a congenital anomaly and suggested the designation "gastric-lined esophagus."

A case report is presented in which the above diagnosis was suggested by barium swallow and confirmed by esophagoscopy with serial biopsy studies at various levels. Inflammatory changes were found in specimens from all 3 zones examined, although no definite ulceration was noted.

The characteristic finding roentgenographically with a barium swallow is a distended "double-sac" appearance of the lower esophagus with a zone of narrowing above and below this dilated portion. The upper area of narrowing corresponds to the junction

of the esophageal squamous epithelium with the heterotopic gastric epithelium; the lower zone of narrowing to the junction of the esophagus with the stomach. A sliding type diaphragmatic hernia may be present. Ulceration may occur in any portion of this segment but generally the most pronounced inflammation and ulceration occurs just proximal to the junction between the stomach and gastric-lined esophagus. The roentgen appearance is pathognomonic, although actual microscopic sections from serial biopsies at various levels are necessary for a definite diagnosis.—*Z. Petrany, M.D.*

Rubinstein, Berta M., Pastrana, Thelma, and Jacobson, Harold G. Tuberculosis of the esophagus. *Radiology*, March, 1958, *70*, 401–403. (From: Montefiore Hospital, 210th St. and Bainbridge Ave., New York 67, N.Y.)

The authors report a case of tuberculous involvement of the esophagus in a patient with advanced bilateral pulmonary tuberculosis.

Esophageal tuberculosis is extremely rare; only 1 case was found in 1,400 autopsies on tuberculous patients performed at the Bellevue Hospital.

Tuberculous infection may reach the esophagus in several ways: (1) Infection of a pre-existing esophageal lesion by tuberculous sputum; (2) extension from laryngeal and pharyngeal lesions by contiguity; (3) extension from caseous hilar lymph nodes or tuberculous spondylitis; and (4) involvement in the course of generalized miliary tuberculosis. The most frequent site of tubercular lesions is the midportion near the bifurcation of the trachea. Symptoms include retrosternal pain and dysphagia. Roentgen findings after barium swallow are ulceration, spasm, alteration and effacement of the mucosal pattern, and stricture formation.

The diagnosis should be suspected when the above findings are present in a patient suffering from pulmonary or miliary tuberculosis.—*John S. Alexander, M.D.*

Abdomen

Sielaff, H.-J. Gastro-intestinale Funktionsdiagnostik mit der Kymo-Kassette. (The kymo cassette in the diagnosis of gastrointestinal function.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1958, *88*, 414–422. (From: Röntgenabteilung der Medizinischen Universitätsklinik, Heidelberg, Germany.)

The author has extended the usefulness of kymography to more precise studies of the esophagus, stomach and duodenum. The kymographic plate with slits at 12 mm. intervals is placed between the tube and the patient, thus reducing the dosage to the patient by approximately 10 per cent. At 60 cm. focal skin distance, with 80–100 kv., at 20 ma., and 2.5 mm. Al filtration, for twenty seconds, the skin dose is 10–20 r for the usual kymographic procedure. The film is in a conventional cassette with highly intensified screens. During the twenty seconds the esophagus, stomach and duodenum will undergo 2–3, 1 and 3–4 intrinsic movements, respectively. Although the slits are magnified about 25 per cent, no significant interference with adequate visualization is encountered.

Esophageal atony was found in patients with osteochondrosis of the cervical and dorsal spine, probably due to damage to the nerves arising from the corresponding levels of the spinal cord. Marked dilatation of the distal end of the esophagus, secondary to chronic esophagitis and perhaps precancerous in nature, is accompanied by total loss of intrinsic movement of the esophagus, while cardiac and respiratory movements are normal. For detailed study of the swallowing act and the cardio-esophageal junction, cinematography is preferable, especially when localized neoplasms are suspected. In these cases, endoscopy is also used.

In the stomach, the chief indication for kymography is in the study of intramural lesions. The specific nature of a tumor cannot be identified, but localized zones of rigidity can be differentiated from extragastric lesions and the attention of the gastroscopist can be directed to these suspicious areas. An infiltrating gastritis does not cause the same degree of mural rigidity as an infiltrating malignant lesion. By the addition of morphine (hypertonic) or buscopan (hypotonic), changes in gastric tonus due to functional disturbances can be evaluated. Thus, by the combination of kymography, cinematography, and pharmaco-roentgenography, more exact indications for surgical intervention may be obtained. Kymography is also valuable in the study of the postoperative stomach to differentiate between recurrences and alterations due to scar tissue and for more detailed study of the "dumping syndrome," the anastomotic site and the dilated jejunal loop.

Investigation of the small bowel has led to the conclusion that there are 2 types of symptom complexes. The atonic type, characterized by nausea, pressure, fullness and meteorism presents dilated, motionless loops of bowel and may be due to: (a) parenchymatous diseases (liver, gallbladder or pancreas); (b) damage of the central nervous system (encephalopathies, brain tumor or generalized cerebral arteriosclerosis); and (c) psycho-vegetative disturbances (endogenous psychosis, generalized vegetative dystonia, etc). The hypertonic type is characterized by scattered zones of increased tonicity and propulsion of the contents of the small bowel and is usually found in the patient referred to as the ulcer-type. Repeated studies have shown that the latter group is a functional and reversible phenomenon. To differentiate this group from the organic enteritides, the author has applied the term "irritation relief pattern" to indicate the functional nature of the condition.—*J. Zausner, M.D.*

Amplatz, Kurt. A new and simple approach to air-contrast studies of the stomach and duodenum. *Radiology*, March, 1958, *70*, 392–394. (From: X-Ray Department, University Hospitals, Minneapolis 14, Minn.)

A new technique for introducing air into the stomach for air-contrast studies is presented. The barium mixture is drunk through a perforated drinking straw which causes the simultaneous introduction of air with the opaque mixture. The size of the perforation must be determined experimentally and depends upon the dilution of the medium employed. A through-and-through perforation with a very small sewing needle, or puncture of one wall with a slightly larger pin is adequate. Usually sufficient air will have entered the stomach after the patient in the upright position has ingested 2 to 3 ounces of the medium.

If the patient is known to have a questionable lesion in the antrum or body of the stomach, the examination is begun in the horizontal left anterior oblique position. After 2 ounces of the barium have been sipped through the straw, the patient immediately assumes the right anterior oblique position for demonstration of the lesion by double contrast. In most cases no contrast material will have entered the duodenum and there will be no superimposition of small-bowel shadows. By turning the patient into different obliquities and changing the tilt of the table, it is possible to demonstrate even very minute lesions of the posterior wall. Lesions of the anterior wall may be obscured by the superimposition of normal posterior wall mucosa. An attempt should be made to demonstrate all anterior wall lesions by double contrast in oblique views with the patient in the prone Trendelenburg position.—*Walter H. Jarvis, Jr., M.D.*

McGee, Andrew R., and Lobb, Ross. Trichobezoar; with a case report. *Radiology*, Dec., 1957, *69*, 860–862. (Address: A. R. McGee, Toronto East General and Orthopaedic Hospital, Toronto 6, Ontario.)

The authors review the interesting history and literature of trichobezoars, some 205 of which have now been recorded.

Bezoars are concretions of foreign material found uncommonly in the stomach and intestines of man and animals. Phytobezoars consist mainly of unabsorbed vegetable residues, while trichobezoars contain hair primarily. In the past, bezoars have been valued as having potent mystic and medical properties, being used as poison antidotes and as restorers of sexual potency.

Trichobezoars may be recognized by fluoroscopic or roentgenographic examination as negative shadows against a background of the opaque medium.

Clinical findings include a secondary anemia and the habit of eating frequent small meals.

The authors present a case report of a trichobezoar removed from the stomach of a twenty-three year old white female who habitually pulled her hair and ate it when excited.—*John Alexander, M.D.*

Ascherman, Stanford W., Bednarz, Wallace W., and Olix, Melvin L. Gastric volvulus; special reference to hepatodiaphragmatic interposition of colon. *A.M.A. Arch. Surg.*, April, 1958, *76*, 621–629. (Address: S. W. Ascherman, 6208th U.S.A.F. Hospital, Clark Air Base, Philippines.)

The authors believe that there are two main types of gastric volvulus, mesenterioaxial and organoaxial. They state that the mesenterioaxial volvulus is the most common and that the rotation takes place from left to right about a vertical axis of the gastrohepatic omentum. The pyloric end passes from right to left, then upward in front of the fundus. A simultaneous opposite movement takes place at the fundus.

The organoaxial volvulus of the stomach consists of two types—one is supracolic and the other is infracolic, depending on the position of the colon. In this type, the rotation is between the cardia and the pylorus. The hepatodiaphragmatic interposition of the colon refers to that condition in which a portion of the colon is located between the right leaf of the diaphragm and the dome of the liver.

The authors have included diagrams and roentgenographic reproductions to illustrate the types. The conditions predisposing to gastric volvulus are reviewed. The treatment is surgical.—*C. Peter Truog, M.D.*

Murphy, Edward S., and Yasuda, Akimasa. Carcinoma of the stomach in Hiroshima, Japan. *Am. J. Path.*, May–June, 1958, *34*, 531–542. (From: The Department of Pathology, Atomic Bomb Casualty Commission, Hiroshima, Japan.)

Carcinoma of the stomach is the most frequent cancer in both men and women in Japan. The authors investigated 535 cases of carcinoma of the stomach which were registered in the surgery, pathology, and necropsy pathology records of the Hiroshima Atomic Bomb Casualty Commission between December, 1948, and June 30, 1957. These cases were analyzed as to whether or not they had been exposed to radiation at the time of the atomic bomb explosion and as to the amount of radiation received.

No significant differences were found in the groups that had been exposed and those which had not been exposed to the explosion of the atomic bomb.—*George L. Sackett, Jr., M.D.*

Cooke, Lorna, and Hutton, Charles F. Postbulbar duodenal ulceration. *Lancet*, April, 1958, *1*, 754–757. (From: Central Middlesex Hospital, London, N.W. 10, England.)

In this article the postbulbar region is considered to be the distal one-third of the horizontal or first portion of the duodenum; *i.e.*, from the distal end of the duodenal bulb to the point where the second portion of the duodenum is directed downward. The junction of the duodenal bulb and the postbulbar region is denoted by a change in the mucosal folds from longitudinal to transverse.

The difficulty of demonstrating the postbulbar region adequately is emphasized. The authors' technique consists of giving a small quantity of barium cream, manipulating this into the bulb and second portion of the duodenum, and then inflating the stomach through a stomach tube. The local stenosis, which is usually present with a postbulbar ulcer, must be distinguished from incomplete filling of the duodenum or constriction due to normal peristaltic waves. The differential diagnosis is considered, including diverticula, adhesive bands, carcinoma of the pancreas, annular pancreas, and malignant and benign tumor of the duodenum.

The features of 25 cases of postbulbar duodenal ulcer are discussed. Of those in which a tentative clinical diagnosis can be made, 2 groups may be separated, the hemorrhagic group and the group with intermittent obstruction.

In postbulbar duodenal ulcer medical treatment is usually unsatisfactory; operation is indicated in most cases, and should be undertaken when the patient is relatively well.—*John F. Weigen, M.D.*

Hilbish, Theodore F., and Black, Roger L. X-ray manifestations of peptic ulceration during corticosteroid therapy of rheumatoid arthritis. *A.M.A. Arch. Int. Med.*, May, 1958, *101*, 932–942. (Address: Public Health Service, National Institutes of Health, Bethesda, Md.)

The authors reviewed their series of 49 rheumatoid arthritis patients on corticosteroid therapy to collect roentgenologic information which would be helpful in diagnosing and treating peptic ulcers induced or activated while on therapy. They found that 12 (24 per cent) had developed peptic ulcers compared with the 5–10 per cent peptic ulceration expected in the general population.

Clinically, these ulcers were characterized by minimal or no symptoms. Pain, if present, though atypical, was still the most reliable symptom, with occult blood in the stool or unexplained rapidly developing anemia occasionally being the first clue. The earliest ulcer appeared after three weeks of treatment, and the latest after six years.

In the medical management of these cases a base line gastrointestinal series is suggested before therapy, in order that roentgenologic deformities in the future may be properly evaluated as to whether they are acute or chronic. Careful questioning concerning epigastric distress and routine stool examinations for occult blood are advised. Suspicion of possible ulceration requires a thorough search for ulcer crater formation.

The authors found that fluoroscopically and roentgenographically: (1) a crater may be the only evidence of ulceration; (2) diminished or absent tenderness to palpation is frequently noted; (3) distortion of tissue around the ulcer crater is often absent, *i.e.*, no edema or radiating mucosal folds are demonstrated; (4) spastic changes, such as an incisura or pylorospasm, are frequently lacking; (5) the slightest fluoroscopic abnormality should be recorded in multiple projections on film; (6) deformed duodenums, in the presence of a previously normal examination, may be regarded as presumptive evidence of an ulcer; and (7) a high index of suspicion is warranted.

The usual treatment included decreasing or stopping the corticosteroids, and placing the patient on an antiulcer regimen.

The complications found included generalized osteoporosis, pathologic fractures, hemorrhages from gastric or duodenal ulcerations, and relatively silent perforations of the upper gastrointestinal tract.—*Donald M. Monson, M.D.*

Lowman, Robert M., and Davis, Leonard. The role of water soluble contrast media in gastrointestinal tract obstruction. *Surg., Gynec. & Obst.*, May, 1958, *106*, 567–572. (From: The Department of Radiology, Grace-New Haven Community Hospital, The Memorial Unit, Yale University School of Medicine, Yale Medical Center, New Haven, Conn.)

According to the authors, barium is not ordinarily used in delineating the point of intestinal obstruction because of the hazards of impaction, peritoneal spill during surgery, and other surgical difficulties.

An ideal contrast medium for determining the point of obstruction should provide adequate contrast, easy administration and have negligible toxicity. It should be easily eliminated and not cause any interference with the surgical efforts to correct the abnormality.

This is a nine month study covering 50 cases with intestinal obstruction. The gastrointestinal tract was examined with water soluble hypaque administered by mouth or by enema.

Because of the known difficulty associated with using thorotrast, lipiodol and iodochlorol, hypaque in powdered form was given orally mixed with carbonated soda water or tap water in concentrations

varying between 10 and 20 per cent. Up to 100 gm. of the powder was used without untoward reaction. Solutions of 12 to 20 per cent were employed as an enema and provided satisfactory results. The contrast medium was never demonstrated to visualize the genitourinary tract. In the majority of cases the material disappeared between twenty-four to forty-eight hours after administration. Despite adequate follow-up, the authors felt it was impossible to get a clear-cut pattern of the absorption of hypaque from the gastrointestinal tract. No exacerbation of diverticulitis was observed.

Though iodinism is a theoretical potential hazard, there was no evidence of this in this study and no evidence of apparent peritoneal irritation was noted following the surgical procedures.

Twenty patients were found to have no obstruction and were subsequently studied with barium with the assurance that the procedure would be safe. The authors feel that the water soluble medium is not a substitute for barium in delineating mucosal pattern, but is a very satisfactory means of demonstrating gross lesions and sites of obstruction when barium is contraindicated.—*Stephen Bruny, M.D.*

Pearson, Seibert C., and MacKenzie, Ronald J. Intestinal obstruction due to bishydroxycoumarin poisoning. *J.A.M.A.*, May 24, 1958, *167*, 455–456. (Address: S. C. Pearson, 117 E. 8th St., Long Beach, Calif.)

Acute abdominal emergencies resulting from the toxic manifestations of anticoagulants have been reported infrequently.

The authors relate an instance of a sixty-nine year old male placed on maintenance levels of bishydroxycoumarin for a diagnosis of thrombophlebitis with pulmonary infarction. After an interval of months and during a period of four weeks, the patient attempted to control his own dosage, sometimes taking up to 200 mg. per day. Subsequently, he was admitted with cramping abdominal pain and hematemesis. Examination disclosed the typical picture of small bowel obstruction and a prothrombin time less than 10 per cent. Following institution of vitamin K_1 oxide therapy and transfusion, abdominal exploration revealed a moderate amount of free blood in the peritoneal cavity. Multiple areas of subserous hemorrhage were seen in the small bowel and marked bowel dilatation was present proximal to an area of massive hemorrhagic infarction in a six inch segment of jejunum. Segmental resection with an end-to-end anastomosis was followed by uneventful recovery.—*James A. Martin, M.D.*

Schapira, Adolfo, Leichtling, Julius J., Wolf, Bernard S., Marshak, Richard H., and Janowitz, Henry D. Diverticulitis of the cecum and right colon: Clinical and radiographic features; report of 18 cases. *Am. J. Digest. Dis.*, May, 1958, *3*, 351–383. (From: The Departments of Medicine, Surgery, and Radiology, and the Gastrointestinal Clinic, the Mount Sinai Hospital, New York, N. Y.)

The authors report 18 cases of this condition. Their findings do not support the common concept that most diverticula of the cecum are solitary. Frequently it is clinically impossible to differentiate between appendicitis and diverticulitis of the cecum, although there may be certain different features in the 2 lesions.

Roentgen study in diverticulitis of the right side of the colon usually shows some delay when the barium reaches the involved area and filling of the ceco-ascending colon may occur in stages. There is commonly a finger like indentation at the site of the lesion intruding into the bowel. The surface of this defect may be spiculated. The defect is not polypoid or lobulated and its base is its widest part. There is no diverticulum within the center of the defect, but one of the spicules may suggest the closed off neck of the diverticulum which was the source of the mural infection. Thickening of the adjacent bowel may extend proximally for a considerable distance. Diverticula may be seen elsewhere on the right side of the colon and occasionally immediately adjacent to the defect. In addition to the discrete defect the adjacent bowel wall shows limited distensibility of a more diffuse nature and when distended it has an irregularly coarsely jagged appearance. In the same projection there may be a surprising constancy of the contour both with barium and with air. Marked segmental or circumferential spasm, so common in sigmoid diverticulitis, is uncommon in cecal diverticulitis. In 2 of the authors' cases which were treated conservatively, re-examination several weeks later showed that the original typical changes had disappeared. However, it is possible that an indentation indistinguishable from a haustral fold may persist.

Conservative nonoperative and operative management is recommended.—*Arthur E. Childe, M.D.*

Wigh, Russell, and Tapley, Norah duV. Metastatic lesions to the large intestine. *Radiology*, Feb., 1958, *70*, 222–229. (Address: R. Wigh, Medical College of Georgia, University Place, Augusta, Ga.)

Metastatic lesions may arise in the colon by way of embolism, direct extension with invasion of the contiguous colon wall or by seeding or implantation of malignant cells. Lesions evolving from direct extension will more closely simulate primary carcinoma, while those produced by seeding or embolization are more likely to be multiple and eccentric in character. The authors, in reviewing 30 cases of metastatic colon lesions, elicited several notable findings, many co-existing, that enable the radiologist to offer the suggestion of metastatic colon lesions with a high de-

gree of confidence. These findings are: a multiplicity of lesions; annular or concentric deformities with conical extremities and the absence of shelving margins; unilateral defects, some with marginal serrations, some with wall pliability; extensive areas of encapsulation and of lobulation; extrinsic pressure defects; uneffaced mucosa; and pathophysiologic changes such as incomplete distensibility with preserved contractility and hypertonicity.

Although primary carcinoma of the colon may be multicentric, metastatic carcinoma causes a much higher incidence of multiplicity of lesions. Over one half the cases reviewed were annular in nature, but the typical shelving margins seen in primary carcinoma were absent. Bowel wall contractility remained, although there was incomplete distensibility. Unilateral defects were produced either by local invasion of one side of the bowel wall, by adjacent infiltration of mesentery, or by implantation of tumor in the serosa. There were only 2 cases of obstruction, but 9 cases revealed partial obstruction to retrograde flow of barium. The bowel was abnormally fixed in 15 cases. Although the mucosa is frequently difficult to evaluate roentgenologically, the authors considered the mucosal pattern to be normal in 20 patients and in none of the cases was effacement sufficient for suspicion of primary malignancy.—*John S. Alexander, M.D.*

MUSSIO-FOURNIER, J.-C., CERVINO, J.-M., RAVERA, J.-J., LORENZO Y LOSADA, H., MAGGIOLO, J., ETCHEVERRIGARAY, D., PEREYRA, E., and VANRELL, R. Hypotonie du colon dans quatre cas de myxoedème de l'adulte; son amélioration par la thyroïde desséchée. (Hypotonia of the colon in four cases of myxedema in adults; its improvement with the use of desiccated thyroid.) *Presse méd.*, April 23, 1958, *66*, 711–712. (From: Institut d'Endocrinologie and Clinique Endocrinologique, Hospital Pasteur, Montevideo, Uruguay.)

Roentgenographic studies on 4 adults with signs and symptoms of myxedema showed long, smooth, tubular colons with considerable diminution to absence of the haustrations. After daily doses of 0.1 gm. of desiccated thyroid for variable periods of time, re-examination showed normal haustral patterns, but no change in the length of the colon.

The authors intend to prolong thyroid therapy in similar cases and anticipate a shortening of the colon. They also point to the literature which describes similar atony of the gallbladder, uterus, urinary bladder, duodenum, etc., in cases of myxedema.—*J. Zausner, M.D.*

GERSHON-COHEN, J., and FISHER, J. F. Contrast enhancement with television technics: Gallbladder lesions. *Radiology*, March, 1958, *70*, 390–391. (From: Albert Einstein Medical Center, Northern Division, Philadelphia 41, Pa.)

The use of television techniques for contrast enhancement and color translation of roentgenograms is described. This technique achieves a contrast enhancement of approximately twenty-fold, permitting discernment of small gallstones or wall-bound papillomata, the presence of which otherwise would not be apparent. Three figures are presented illustrating this technique.—*Donald N. Dysart, M.D.*

EELKEMA, H. HARRISON, STARR, GRIER F., and GOOD, C. ALLEN. Partial duplication of the gallbladder, diverticulum type; report of a case. *Radiology*, March, 1958, *70*, 410–412. (From: Mayo Clinic, Rochester, Minn.)

Duplications of the gallbladder may be classified into 3 main types: (a) Double gallbladder (two cystic ducts); (b) bilobed (one cystic duct draining a bifid viscus); and (c) diverticulum. These anomalies are rare in man, particularly the bilobed and diverticulum types.

The authors report a case of the diverticulum type of partial duplication of the gallbladder. Mucous glands resembling those usually found only in the cystic duct and neck of the viscus were demonstrated in the neck of the ostial portion of the diverticulum.—*Donald N. Dysart, M.D.*

ANSAY, J. (Bruxelles, Belgium.) Réflexions à propos de 1,000 cholécystographies avec étude volumétrique et courbe de cholecystocontraction. (Considerations on 1,000 cholecystographies with volumetric study and curves of gallbladder contractions.) *J. belge de radiol.*, No. 1, 1958, *41*, 1–12.

The patient is asked to eat a fat-rich meal at noon (to help evacuate the gallbladder). At 2 P.M. he is given 6 tablets (3 gm.) of telepaque. At 5 P.M. he is allowed to have a light meal devoid of fat. At 6 P.M. he is asked to swallow another 6 tablets of telepaque and abstain from food until cholecystography is performed the next morning. The focus-film distance is 80 cm., the patient standing in a slightly left anterior oblique position. The volume of the gallbladder is measured by the Siffert grid. All patients are given a standardized fatty meal (Bladex mixed with water) and roentgenographed in the same upright position fifteen minutes, one hour and two hours after ingestion. Thus the correction factor would be the same for all films of the same patient as regards computation of the gallbladder volume.

Of these 1,000 gallbladder cases, 107 were anomalous or cholelithiasic and hence were not considered in the analysis as to normal function. Of the remaining 893 cases, 701 (approximately 78 per cent) showed a progressively increased contraction of the

gallbladder after the fatty meal. Approximately, the gallbladder contracted 50 per cent at the end of fifteen minutes, 75 per cent at the end of one hour, and 80 per cent at the end of two hours. After two hours it began to dilate, at times attaining a size larger than its preprandial volume. The mean volume of the gallbladder before the fatty meal was 37 cc. It was 21 cc. fifteen minutes after the meal; 12 cc. one hour and 8 cc. two hours after the meal. These are relative values and the author considered abnormal those cases where there was considerable variation from these figures. These abnormal cases amounted to about 22 per cent of the 893 cases.

The author divides the abnormal cases into six groups: (1) Compensated dyskinetic gallbladders (93 cases) which showed considerable dilatation after the initial contraction of the first postprandial hour; (2) decompensated dyskinetic gallbladders (51 cases) which contracted inadequately during the first hour and then dilated considerably; (3) atonic or decompensated gallbladders (28 cases) which contracted very slightly and dilated soon after the fatty meal; (4) hyperkinetic or intolerant gallbladders (9 cases) which contracted very rapidly and completely on fatty meal stimulus; (5) bilious or truly hypertonic gallbladders (6 cases) which exhibited a globular and hypertonic contour and which did not contract after the fatty meal; and (6) anatomically abnormal gallbladders (5 cases) such as double and bilocular gallbladders.

Of the 107 cases which showed gallstones 60 per cent reacted normally to the fatty meal stimulus, whereas the remaining 40 per cent fell under several of the above abnormal groupings. Of these, 5 cases had cholesterine inclusion type of mucous pseudopolyps (strawberry gallbladder).—*Jiriar N. Sarian, M.D.*

Gynecology and Obstetrics

Cope, Ian, and Murdoch, J. Duncan. The estimation of foetal maturity. *J. Obst. & Gynaec. Brit. Emp.*, Feb., 1958, *65*, 56–57. (From: Institute of Obstetrics and Gynaecology, Hammersmith Hospital, London, England.)

It has been suggested that the reported variations in the time of appearance and rate of development of certain ossification centers might be largely due to errors in the estimates of the maturity of the infants examined. The evidence from this small series of twin pregnancies shows that wide variations in ossification do, in fact, occur in infants of equivalent true gestation age.

Where the difference was marked, in 2 cases the female twin showed more advanced ossification than the male, which accords with previous observations in singlets of apparently similar gestation age; in a third case of marked difference in ossification in male twins, the more advanced development occurred in the fetus of substantially greater weight.

The presence of advanced ossification in a premature female, with average ossification in its male twin, at the age of thirty-seven weeks, suggests that true postmaturity cannot be recognized by the degree of epiphyseal ossification.—*Eugene J. McDonald, M.D.*

Poidevin, L. O. S., and Bockner, V. Y. A hysterographic study of uteri after caesarean section. *J. Obst. & Gynaec. Brit. Emp.*, April, 1958, *65*, 278–283. (From: Department of Obstetrics, University of Adelaide, Adelaide, So. Australia.)

The authors studied a group of women to determine if there was any appreciable change in the roentgenographic appearance of the uterus following cesarean section. Forty-three postcesarean examinations were done and 13 normal vaginal delivery uteri were studied.

Attention was paid to the degree of scarring or other deformity following cesarean section in an attempt to evaluate the question of whether or not a previous cesarean section is necessarily an indication for a repeat section in the absence of a persistent or recurring sign, such as pelvic contraction.

The uterus was injected with radiopaque material and roentgenograms were made first in the lateral projection and subsequently in the anteroposterior projection. They revealed some degree of deformity in every uterus which had been subjected to cesarean section. The most common was a wedge-shaped projection extending outward from the lumen of the uterus and indicated that this represented the area of the previous incision. The authors demonstrated no relationship between the size of the deformity and the various clinical factors which might be considered.

They arbitrarily divided the cases into groups showing small (under 5 mm.) and large (6 mm. or more) deformities. They felt that any case showing a large deformity should probably have a repeat cesarean section.—*George L. Sackett, Jr., M.D.*

Ferreira, H. P., and Clayton, S. G. Three cases of malignant change in endometriosis, including two cases arising in the rectovaginal septum. *J. Obst. & Gynaec. Brit. Emp.*, Feb., 1958, *65*, 41–44. (From: Chelsea Hospital for Women and King's College Hospital, London, England.)

The possibility of malignant change in endometriosis of the ovary has been discussed in numerous papers published since 1925, when Sampson described 7 cases of ovarian carcinoma in which adjacent endometrial tissue could be seen. In 4 of these cases, he suggested that the carcinoma arose as a secondary change in a benign endometrial cyst. The

difficulty of establishing that a carcinoma has arisen in this way is well recognized and subsequent writers have been more critical.

To be satisfied that a malignant growth has arisen in an endometrioma, the following criteria may be necessary: (1) The malignant tumor must be in direct relationship to the endometrioma, and preferably direct transition between the endometrioma and carcinoma should be seen; (2) no other primary site of malignant disease should be evident; and (3) the histologic appearance of the malignant growth should be such that its origin from an endometrioma is possible.

It is likely that many other surgeons have encountered single cases of carcinoma arising in ovarian endometrioma and have not reported them, although judging from the infrequency of such reports in the literature this must be a very rare type of cancer.

There is a possible alternative explanation for these cases, but one that does not seem so probable. Bonney and Glendining (1910) first described the condition of adenosis of the vagina, in which mucinous glands are found in the vaginal wall. Plaut and Dreyfuss (1940) mentioned the possibility of adenocarcinoma arising in such cases. In the present material there was no evidence of this condition.—*Eugene J. McDonald, M.D.*

Brown, George R. Acute hydramnios treated by abdominal paracentesis; case report. *J. Obst. & Gynaec. Brit. Emp.*, Feb., 1958, *65*, 61–63. (From: Lennox Castle Maternity Hospital, Glasgow, Scotland.)

Acute hydramnios is a rare complication of pregnancy. Both from a review of the literature and from his own experience, Mueller (1948) concluded that the incidence was about 1 in 12,500 pregnancies.

The following is the report of a case in which a healthy mature child and a fetus papyraceus were delivered sixteen weeks after amniotomy had been performed by abdominal paracentesis on account of acute hydramnios.

Amniotomy by abdominal paracentesis should be considered in the treatment of acute hydramnios occurring in the middle trimester of a plural pregnancy for, unlike other methods of treatment, it occasionally allows the pregnancy to continue until the delivery of a normal viable child. Moreover, it may cause less disturbance to an acutely ill and orthopneic patient and involve less risk of intra-uterine infection than puncture of the membranes per vaginam. The procedure seems to be quite safe provided reasonable precautions are taken to avoid vital structures.

In the present state of knowledge amniotomy by abdominal paracentesis seems to be a rational method of treatment in a case such as the one described in which at least 1 fetus appeared normal on the roentgenogram. It is of interest to note that, while the presence of signs of fulminating toxemia in the case described might have justified termination of the pregnancy, these toxemic signs disappeared permanently following the removal of 6 pints of liquor amnii.—*Eugene J. McDonald, M.D.*

Genitourinary System

Strandness, D. E., Jr. The unilateral nonfunctioning kidney. *A.M.A. Arch. Int. Med.*, March, 1958, *101*, 611–619. (Address: 4021st U.S.A.F. Hospital, Dyess Air Force Base, Abilene, Texas.)

Seventy cases of unilateral nonfunctioning kidney by intravenous pyelography were reviewed in detail. Extrarenal lesions were readily diagnosed by the combination of abdominal roentgenography, cystoscopy, and retrograde pyelography. Diseases of the renal parenchyma presented more of a problem and the following criteria were given: A kidney of normal size and architecture without function suggests renal artery thrombosis. A kidney of small size with normal architecture and without function suggests hypoplasia or renal artery thrombosis. A kidney of small size without function and with abnormal architecture suggests atrophic pyelonephritis or hypoplasia. Agenesis or aplasia is suggested if the ureteral orifice is missing, but ectopic implantation or inflammatory obliteration of the ureter must be kept in mind especially if no abnormality of the trigone is found. Retrograde pyelography will usually confirm the diagnosis of neoplasms, tuberculosis, and congenital malformation of the pelvis or ureter. Aortography may aid in the diagnosis of neoplasms, renal artery thrombosis, aberrant renal artery, and agenesis. Retroperitoneal air studies were seldom necessary.—*Arch H. Hall, M.D.*

Barquín, F., Blanco, P. Leon, Senra, J., and Barquín, Otto. Hipertensión nefrógena por osificación de la arteria renal derecha. (Renal hypertension caused by ossification of the right renal artery.) *Arch. méd. de Cuba*, Sept.–Oct., 1957, *8*, 281–288.

A white female, aged thirty-five, was admitted to the cardiac service with a picture of acute cardiac insufficiency. A hypertension of 220/125 was found, with a pulse rate of 120. Roentgenologic examinations and pyelograms disclosed a calcification in the region of the right renal artery. Kidney function tests were normal. Exploration showed that the walls of the right renal artery were very hard.

On pathologic examination, the renal artery was found to be larger than normal and of such firm consistency that it gave the sensation of palpating a tube. A roentgenogram of the extirpated kidney showed that the artery was calcified and penetrated deeply into the renal parenchyma, dividing into several branches. Pathologically, the walls of the

renal artery were not calcified as first suspected, but formed a tube of bone, in the center of which there was marrow, such as found in ordinary bone.

A diagnosis was made of renal hypertension as the result of ossification of the right renal artery and ischemia of the kidney. This was considered to be similar to the experimental renal hypertension described by Goldblatt and associates in 1934. The follow-up examination of this patient over a period of five years confirmed the diagnosis.—*Murray M. Friedman, M.D.*

Tatelman, Maurice, and Pakusch, Rainer S. A comparative evaluation of the newer contrast media for excretory urography. *Radiology*, Feb., 1958, *70*, 238–252. (Address: 1326 St. Antoine, Detroit 26, Mich.)

A comparative study of the results of a total of 1,726 examinations of the urinary tract was undertaken. Hypaque 50 per cent, urokon 50 per cent, neo-iopax 50 per cent, miokon 50 per cent and renografin 76 per cent were the contrast media used. Technique of examination was the same in all cases and the roentgenograms obtained were evaluated without prior knowledge of the compound employed. The roentgenographic quality and the contrast produced by the excreted material were carefully evaluated. Any local or systemic reaction, no matter how mild, was noted.

The results showed that the incidence of reactions, particularly nausea and vomiting and arm and shoulder pain, was definitely lower with hypaque and renografin than with the other compounds investigated. Miokon afforded a slightly higher percentage of excellent pyelograms than any of the other media. The number of satisfactory and excellent studies obtained with neo-iopax was significantly lower. In the authors' opinion, hypaque and renografin are the most satisfactory contrast media available when the factors of both patient tolerance and roentgenographic quality are considered.—*Donald N. Dysart, M.D.*

Garfinkel, Burton, and Furst, Nathan James. Simultaneous roentgen examination of the urinary and biliary tracts with duografin. *Radiology*, Feb., 1958, *70*, 243–246. (Address: B. Garfinkel, U. S. Army Hospital, Fort Jay, N.Y.)

Duografin is a new roentgenographic contrast medium which contains 40 per cent renografin for urography and 20 per cent cholografin for cholecystography and cholangiography. Both media are present as the methylglucamine salt in aqueous solution.

Indications for the use of duografin include all of the indications for pyelography and intravenous cholecystocholangiography. It is further indicated in acute abdominal diagnostic problems when symptoms point to the right upper abdominal region, especially when time is an important factor in diagnosis and treatment. It is also of value in routine examinations to save time and radiation exposure of the patient. Its use eliminates the necessity of separate intravenous injections for each examination and avoids the necessity of 2 separate preparations.

The authors report their experiences with the use of this medium in 25 patients. None exhibited any severe reactions to the medium and the few that had mild nausea and some mild retching, responded immediately to 20 mg. of benadryl given intravenously. All showed good urinary tract visualization. Sixteen showed good visualization of the gallbladder. Of the remaining 9, 4 had had previous cholecystectomies, and in 3 of these, the bile duct was well visualized. Four of the other 5 with no visualization of the gallbladder and bile duct had liver or bile duct pathology to account for this. The only contraindications to the use of duografin are a sensitivity to the test dose and severe impairment of renal and liver function.—*Donald N. Dysart, M.D.*

Skeletal System

Haraldsson, Stefan. The intra-osseous vasculature of the distal end of the humerus with special reference to capitulum; (preliminary communication). *Acta orthop. Scandinav.*, No. 2, 1957, *27*, 81–93. (From: The Orthopaedic Clinic, Lund Hospital, Lund, Sweden.)

Because of its relation to osteochondrosis capituli humeri the author studied the intra-osseous vasculature of the distal end of the humerus. The vascular systems of 15 cadavers from three months to seventy-five years of age were injected with a mixture of white lead and gum arabic in water. The distal end of the humerus was excised fifteen minutes after the injection and was fixed in 5 per cent formalin for twenty-four hours. The periosteum and the soft parts were removed and sterescopic angiograms were taken. The specimen then was placed in Jenkins' fluid. The decalcification process was followed roentgenologically.

The author concludes that as long as the nucleus of ossification of the capitulum of the humerus lies isolated in the epiphyseal cartilage, it appears to receive its blood supply via a few vessels entering the cartilage from behind and forming intercommunicating vessels in the nucleus of ossification. At this period there is no communication of the vessels of the nucleus with the other segments of the distal end of the humerus. The nucleus of the capitulum humeri extends into the radial part of the epiphyseal cartilage of the trochlea, thus contributing to the ossification of the trochlea. Before sufficient bone salts are deposited for roentgen visualization, vessels are evident in the future site of the ossification nucleus of the trochlea. The vascular pattern formed in the capitulum during ossification persists unchanged into adult bone. The blood vessels of the diaphysis, metaphysis

and epiphysis intercommunicate after ossification of the cartilage between the various nuclei of ossification of the epiphysis and of the epiphyseal plate.—*J. N. Ané, M.D.*

Kerin, Robert. Metastatic tumors of the hand. *J. Bone & Joint Surg.*, April, 1958, *40-A*, 263–278. (From: The Department of Orthopaedic Surgery, Western Reserve Medical School and the Veterans Administration Hospital, Cleveland, Ohio.)

Twenty-three cases of malignant tumor metastatic to the hand are summarized and 7 new cases added. In 2 of the cases metastases appeared in the soft tissues of the hand first, with secondary involvement of the underlying bone; one of these was primary in the kidney and the other a chorionepithelioma of the testicle. Sixteen of the 23 cases in the literature showed findings that made diagnosis certain and in the other 7 the diagnosis was made on clinical and roentgenographic basis.

The terminal phalanges were involved more often than the other bones and there was only 1 case of carpal invasion. More than twice as many males were affected as females. Almost 50 per cent of the cases had the primary neoplasm in the lung and in some of these, the metastasis in the hand was the first indication of silent pulmonary neoplasm. Breast, kidney and parotid were the next most common primary sites. Metastatic tumors to the foot are rare, but more frequent than to the hand.

In a large number of cases an acute inflammatory lesion was the presenting complaint and the initial diagnosis was whitlow, felon or acute osteomyelitis. The destructive process rarely crosses the joint space to involve the adjacent bone.

Several benign bone tumors are listed, but these are not easily confused with metastatic tumors. New bone formation in osteogenic sarcoma or Ewing's tumors should differentiate these from metastatic lytic lesions.

The fact that the hand is not generally included in a metastatic survey may partially account for the small number of recorded cases.—*Martha Mottram, M.D.*

Korttila, Kaleva, and Meurman, Lauri. Eosinophilic granuloma of bone; report of two cases with vertebra plana. *Acta orthop. Scandinav.*, No. 2, 1957, *27*, 94–114. (From: The Surgical Clinic, and The Institute of Pathological Anatomy, University of Turku, Turku, Finland.)

The authors report two cases of eosinophilic granuloma with multiple bone lesions which occurred in children of one year seven months and of two years three months of age, respectively.

In the first case, there was involvement of the right femur, the right and left ribs, the first lumbar body, the ilium and the skull. Eosinophilia was not noted during the first six months of the course of the disease. After nine months of illness the child began to show signs of clinical recovery. At the end of another period of five months clinical recovery was complete. The right leg was shortened by 1 cm. as the result of an old pathologic fracture of the right femoral neck. There was residual anterior wedging of the first lumbar body, without gibbus. The intervertebral spaces were intact. All bone lesions were healed and no new lesions were noted. Therapy consisted of immobilization, blood transfusions, vitamins and roentgen therapy.

In the second case, there was a definite history of injury five months before admission of the child to the hospital. Roentgenograms showed an osteolytic process involving the tenth thoracic body, and later a similar process was noted in the fifth thoracic body. These vertebral bodies were wedged and showed thin tapering formations anteriorly beyond the anterior surfaces of the remaining thoracic bodies. The intervertebral spaces were intact. Similar lesions were noted in the left pubis and the left parietal bones. The active phase of the disease lasted approximately three months and the total duration of the disease about seven months. Eosinophilia was noted in the peripheral blood three months after onset. Therapy consisted of ACTH, methylandrostendiol and prednisolon.

The differential diagnosis of vertebral eosinophilic granuloma is concerned with tuberculous spondylitis and vertebra plana. In tuberculous spondylitis the intervertebral spaces are involved and gibbus results. The center of the vertebral body is not affected in eosinophilic granuloma and the wedge-like tapering body extends beyond the line of the vertebral bodies. The authors believe that these two cases support the assumption of other workers, notably of Calvé, that vertebra plana may be caused by eosinophilic granuloma.

In the present studies, bone changes were noted on roentgenograms surprisingly early. On the other hand, the blood picture, blood chemistry, and bone marrow puncture offered no help in diagnosis.

The etiology of eosinophilic granuloma is not clear although trauma may be a factor. Of interest, in the authors' cases was the presence of the relatively large amount of iron-free pigment. As interpreted by the authors, the results of the present study do not support the theory classifying eosinophilic granuloma of the bone as the benign form of Hand-Schüller-Christian disease or Letterer-Siwe disease. Roentgen therapy, ACTH and prednisolon showed favorable results on the course of the disease.—*J. N. Ané, M.D.*

Gee, Vernon R., and Pugh, David G. Giant-cell tumor of bone. *Radiology*, Jan., 1958, *70*, 33–45. (Address: V. R. Gee, 1348 Market St., Redding, Calif.)

The authors report the results of a study of 104 lesions meeting current criteria for the pathologic diagnosis of giant-cell tumor of bone. All patients were seen at the Mayo Clinic up to January, 1955. Pain was a feature in 98 of the 104 cases in this series, and swelling in 78. A mass was palpable in 88 cases. Symptoms had been present for periods ranging from a few days to three years. Only 9.6 per cent of patients were less than twenty years old and 24 per cent were more than forty. The youngest patient was twelve years old, and the oldest seventy-one at the time of diagnosis. There were 58 females and 46 males. Eighty-four per cent of the tumors occurred in long bones of the extremities. Histopathologic proof of malignancy was obtained in 9 of the series (9 per cent). In 2 of these, areas of fibrosarcoma were found in otherwise typical giant-cell tumors at the initial examination. In the remaining 7 cases, malignant lesions were demonstrated from four to fourteen years after the original diagnosis of giant-cell tumor. In 7 additional cases the course of the disease suggested the possibility of malignant transformation.

Epiphyseal union had occurred in all but 3 of the 67 cases in which roentgenograms of the long bones were available. In one of these 3 cases, the lesion was confined to the metaphysis and in the other 2 the lesion extended across the epiphyseal plate. In the remaining cases the lesion was located in the end of the bone. The lesion was situated eccentrically with reference to the long axis of the bone in 78 per cent of the series. Expansion of the external osseous margin was absent or questionable in 23 per cent, slight in 19 per cent, moderate in 41 per cent, and marked in 17 per cent of the cases. The peripheral margin of the tumor was usually at least partially encompassed by a thin bony shell. Defects in this shell were present in nearly half of the cases. A prominent trabeculated pattern was present in 49 per cent of the cases. An additional 21 per cent had minimal evidence of trabeculation.

The sacrum and ilium were the flat bones most commonly involved. Expansion was present in only a third of the involved flat bones. A bony shell enclosing the margin of the tumor was demonstrable less often than in the long bones, and the bony shell was more likely to be incomplete. Trabeculation was not a prominent feature of giant-cell tumor of the flat bones. Tumors involving the pelvic bones were easily overlooked in a study of the roentgenograms.

Lack of correlation of the initial roentgen picture of the giant-cell tumor with the course of the disease after treatment and with the variation in microscopic features is emphasized.—*Arno W. Sommer, M.D.*

Deibert, Kirk R. (Florence, Ala.) Lytic lesions of ribs. *South. M. J.*, April, 1958, *51*, 523–528.

The author observed 71 cases having lytic lesions of the ribs over a nine year period. Some of the clinical and roentgenologic features of the various categories are discussed.

There are 26 categories listed, namely: 1. Myeloma (7 cases); 2. reticulum cell sarcoma (2); 3. Potts' disease—tuberculous spondylitis and involvement of rib posteriorly (6); 4. carcinoma of lung—metastatic (9); 5. hypernephroma—metastatic (6); 6. malignant melanoma—metastatic (1); 7. carcinoma of breast—metastatic (2); 8. carcinoma of thyroid—metastatic (1); 9. carcinoma—metastatic of unknown origin, 1 superior sulcus tumor (3); 10. coarctation of aorta—notchings (2); 11. undulated wavy notching, old inflammatory reaction (3); 12. tuberculous costochondritis (4); 13. actinomycosis (1); 14. blastomycosis (1); 15. Ewing's sarcoma (1); 16. polycythemia (1); 17. leukemia (1); 18. fibrous dysplasia (5); 19. aortic aneurysm (1); 20. eosinophilic granuloma (1); 21. cyst or enchondroma (6); 22. osteochondroma (1); 23. giant cell tumor (1); 24. Pancoast syndrome (2); 25. osteomyelitis and periostitis, postempyema inflammation (2); 26. fragilitas ossium (1).—*C. Peter Truog, M.D.*

LaFond, Edward M. An analysis of adult skeletal tuberculosis. *J. Bone & Joint Surg.*, April, 1958, *40-A*, 346–364. (From: Glen Lake Sanatorium, Oak Terrace, Minn.)

Two hundred and thirty cases of adult skeletal tuberculosis in the prestreptomycin years were studied and compared with a group of 196 proved cases which received streptomycin, 1 gram a day for 4 months, and a group of 40 cases receiving drug therapy up to a year, often with para-aminosalicylic acid as a second drug.

The bone lesions were preponderantly in males and almost half the patients were between seventeen and thirty-five years of age. The commonest sites of involvement were the spine and the major weight-bearing joints. Fifty-one per cent of the patients had active pulmonary tuberculosis, 20 per cent had genitourinary tuberculosis and 13.5 per cent pleural effusion. Multiple lesions were common (1.26 active lesions per patient). Draining sinuses were present in almost 40 per cent of cases. When the sacroiliac joint was involved, there was a higher percentage of multiple skeletal lesions and an increased mortality rate.

The factors which were associated with an increased mortality rate were the location of the lesion, its extent, the multiplicity of foci and the presence of pulmonary tuberculosis.

The roentgenographic course in the patients with adequate films was studied by a jury of 3 orthopedists. The conclusions drawn are that there "appeared to be improved healing of the bone lesions in patients who had been treated with streptomycin. The effect of streptomycin on tuberculous osteomyelitis from a roentgenographic standpoint is not clear . . . and spread of bone infection or new bone lesions have been observed while the patient was receiving

streptomycin." The effects of streptomycin on soft-tissue tuberculosis are considerable.—*Martha Mottram, M.D.*

Oberniedermayr, A. Epiphysäre Erkrankungen im Kindesalter. (Epiphyseal diseases in childhood.) *München. med. Wchnschr.*, April, 4, 1958, *100*, 571–523. (Address: Chir. und Orthop. Abt. der Univ.-Kinderklinik, Lindwurmstr. 4, München 15, Germany.)

The author has classified epiphyseal diseases in children into two groups: (1) Primary birth traumatic epiphyseal displacement, dysplasia of ossification nucleus in congenital dysplasia of the hips, aseptic necrosis and osteochondritis dissecans; and (2) secondary changes in the epiphyses in systemic disease, syphilis, osteomyelitis, juvenile epiphyseal displacement, and growth disturbance of the epiphysis in paralysis as a result of failure of function.

Most frequently involved are the proximal epiphysis of the humerus and femur. The roentgen study shows an abnormal position of the neighboring bony parts in relation to the cartilaginous head as compared to the normal joint. Epiphyseal dislocation of the femur is characterized by the same findings as congenital dislocation of the hip: high position of the tip of the trochanter and increase in distance of the trochanter, but in contrast to dislocation, there is a normal acetabulum. One must attempt immediately to approximate the dislocated epiphysis to the metaphysis in as near normal position as possible. In congenital dislocation of the hip, in addition to the shallowness of the acetabulum, the dysplasia of the proximal epiphysis of the femur plays a prominent role. Roentgen findings in Perthes' disease of the hip are widening of the joint space, sclerosis and later a flattening of the femoral head, and bone defects in the femoral neck and acetabulum. In Scheuermann's disease of the spine, the vertebral borders are irregular and spotty, the contour of the superior margins of the bodies is hazy and in the later stages shows indentations.

The secondary epiphyseal diseases are the result of various systemic diseases of the body. For example, there is retardation in development of the epiphyses in hypothyroidism, celiac disease, and avitaminosis.—*Samuel Richman, M.D.*

Ackerman, Lauren V. Extra-osseous localized non-neoplastic bone and cartilage formation (so-called myositis ossificans). *J. Bone & Joint Surg.*, April, 1958, *40-A*, 279–298. (From: The Barnard Free Skin and Cancer Hospital, Barnes Hospital, and Washington University School of Medicine, St. Louis, Mo.)

Localized typical myositis ossificans is usually observed in young males following trauma and is often located around the knee or anterior aspect of the arm. Calcification occurs after the development of osteoid and finally well oriented bone is formed. Calcification may appear within three to four weeks following trauma.

Periosteal bone proliferation is often considered an indication of malignancy, but these changes may be associated with myositis ossificans, infection, trauma, subperiosteal hemorrhage, granulomata, lues or benign bone tumors. In some of these cases, the history, clinical findings and roentgenographic features may establish the diagnosis, but in most instances, a biopsy is necessary.

Large tumor-like masses in atypical locations may be difficult to interpret and are often misdiagnosed as sarcoma. Four of these cases were in the buttock, and one in the upper arm, and all were originally diagnosed as osteosarcoma. There were firm, formed masses and the underlying bone was not involved, All patients did well and are free of disease after fifteen months to five years. The diagnosis was made by biopsy. In these benign lesions, Ackerman recognizes three zones: (1) The inner zone is very cellular with variation in the size and shape of cells, the mitotic activity being indistinguishable from that of sarcoma; (2) the middle zone shows oriented osteoid tissue; and (3) the outer zone has well-formed bone.

The microscopic evaluation of these lesions would be impossible if tissue were taken from the central area or in the first three to four weeks when there has not been time for orientation or new bone formation to occur in the periphery. Different degrees of maturation exist with the best differentiated zone at the periphery. In the older lesions well formed bone is present throughout, and if not removed, there will be progressive orientation and maturation of the bone with the formation of a cartilaginous cap so that grossly and microscopically, it appears as an osteochondroma. Some ossifications completely disappear or regress due to osteoclastic absorption. The author states that he has never seen a myositis ossificans turn malignant. Zone phenomena do not occur in soft tissue sarcomas, nor is there any well oriented bone.—*Martha Mottram, M.D.*

Schraer, Harald. Variation in the roentgenographic density of the os calcis and phalanx with sex and age. *J. Pediat.*, April, 1958, *52*, 416–423. (From: Biophysics Laboratory, The Pennsylvania State University, College of Chemistry and Physics, University Park, Pa.)

Using standardized roentgen organs, the x-ray density coefficients of the left os calcis in 738 boys and 746 girls, and the middle and end sections of the second phalanx of the left fifth finger in 395 girls and 624 boys, all between the ages of seven and twenty years, were measured.

The mean density coefficient of both bones is said

to increase significantly with age in both sexes except for the os calcis trace path of the females between the age groups thirteen, fifteen, and sixteen through twenty, and the phalanx center trace path of the males between the age groups seven through nine and ten through twelve.

The phalanx shows higher density coefficients than the os calcis in both sexes.

The phalanx density coefficients of the females are significantly greater than those of the males of the same age and, except for the seven through nine year age group, the os calcis values of the males are significantly greater than those of the females.—*James J. McCort, M.D.*

Bernstein, Charles, Loeser, William D., and Manning, Leo E. Erosive rib lesions in paralytic poliomyelitis. *Radiology*, March, 1958, *70*, 368–372. (From: Chronic Disease Research Institute, 2183 Main Street, Buffalo, N.Y.)

A previously undescribed erosive rib lesion has been observed by the authors on chest roentgenograms of paralytic poliomyelitis patients. Fourteen of 28 cases presented showed this lesion. The third rib was involved most frequently, usually bilaterally although the second, fifth, seventh and eighth ribs also showed involvement in some cases.

The earliest change appeared as a localized shallow indentation and narrowing of the upper rib margin followed by progressive thinning and osteoporosis of the involved segment. In the most severe cases almost total disappearance of bone structure occurred. The changes usually appeared ten to twenty months after the onset of paralysis. The most severely paralyzed patients showed the greatest frequency of involvement.

The bone erosion is ascribed to the continued pressure of the medial margin of the scapula against the posterior aspect of the rib causing a pressure necrosis. The reason for some patients being spared is not yet determined. There are usually no associated clinical signs or symptoms.—*Z. Petrany, M.D.*

Gougleris, K., Swoboda, W., and Wolf, H. G. Veränderungen der Wirbelsäule im Verlauf der Leukämie beim Kind. (Involvement of the vertebral column by leukemia in children.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, March, 1958, *88*, 309–318. (Address: K. Gougleris, Sidirokastron, Greece; and W. Swoboda, and H. G. Wolf, Univ.-Kinderklinik, Lazarettgasse 14, Wien 9, Austria.)

Leukemic changes in the skeleton of children have been well described, especially in the bones of the extremities. Involvement of the vertebrae by leukemia has been noted much less often.

Five cases of leukemia of the vertebral column are described. In two cases there were localized areas of destruction with partial collapse and deformity of the bodies. Not all vertebral bodies need be involved. Another type of involvement is a diffuse osteoporosis; usually the entire vertebra is uniformly involved and there may be collapse of some vertebrae. At times there are back symptoms as the primary complaint in such cases. Involvement of the spine without findings in the bones of the extremities seems to be a rare occurrence.

Cortisone therapy may cause a marked osteoporosis and some collapse of the vertebral bodies; and the differential diagnosis between cortisone effect and leukemic involvement may become very difficult at times.—*Hans W. Hefke, M.D.*

Henrichsen, Erik. Bone formation and calcification in cartilage. *Acta orthop. Scandinav.*, No. 3, 1958, *27*, 173–191. (From: The Biological Institute of the Carlsberg Foundation, Copenhagen, Denmark.)

By histochemical means the alkaline phosphatase which appears in the cartilage cells during hypertrophy was found to be related to the degree of cell degeneration.

Calcification in cartilage occurred when the phosphatase containing cartilage cells died, whereas living cartilage cells, even if they contained alkaline phosphatase, were not accompanied by calcification.

This relationship between cell degeneration, alkaline phosphatase activity, cell death, and calcification in cartilage is similar to that found by the author to occur in tissue cultures of fibroblasts and in tuberculous lymph nodes.

The amount of alkaline phosphatase which appears in osteoblasts was related to the degree of cell differentiation.—*James J. McCort, M.D.*

Steffensen, Johs. Chr. A., and Evensen, A. Bursitis retrocalcanea achillis. *Acta orthop. Scandinav.*, No. 3, 1958, *27*, 228–236. (From: Surgical and Roentgenological Dept. of Gjøvik Flykessykehus, Gjøvik, Norway.)

This syndrome, also known as achillodynia, calcaneal spur and tendinitis, is described as occurring most frequently in military personnel or in others who do much occupational walking. Pain in the heel is aggravated by direct pressure, excessive walking, poorly fitting shoes or direct squeezing of the Achilles tendon. A feeling of tension in the tendon enforces rest of the foot, usually in equinus position. Pathologic changes have been found varying from mild aseptic inflammation in the bursa between the upper posterior surface of the calcaneus and the Achilles tendon to actual osteitis and hypertrophic changes in the posterior surface of the bone itself.

The authors describe 3 configurations on lateral soft-tissue roentgenograms of the foot which they feel

are predisposing factors in this syndrome. These are an increase in the lever angle of the calcaneus, prominence of bone on the upper posterior surface of the calcaneus and the altered relationship of the Achilles tendon in the presence of these factors. The lever angle is defined as that angle formed between a line drawn from the calcaneal tuberosity or upper point of Achilles insertion to the deepest point of the sinus tarsi, and a second line from the tuberosity to the upper, hindmost point of the posterosuperior edge of the calcaneus. Whereas the average angle is given as 60 degrees, anything of 63–65 degrees or more is considered excessive. Study of the heel bones in 250 random roentgenograms taken from department files disclosed 7 cases of significant alterations in these factors. Clinically, all 7 were found to have various degrees of symptomatology from previously undiagnosed bursitis retrocalcanea achillis.

Treatment of the lesion depends upon severity of symptoms. Roentgen therapy has given temporary relief only. In severe cases, radical surgery is recommended employing a lateral approach sparing the Achilles tendon and excising the bursa and any existing bony prominence over which the tendon rides.—*James A. Martin, M.D.*

Blood and Lymph System

McAfee, John G. Complicaciones de la aortografía abdominal. (Complications of abdominal aortography.) *Radiología, Panamá*, March, 1958, *8*, 53–56. (From: Department of Radiology, Johns Hopkins Hospital, Baltimore, Md.)

A total of 13,207 aortograms served as a basis for the study of complications of abdominal aortography. In 375 cases, a femoral retrograde sound was also used. Death occurred in 37 cases or 0.28 per cent. Ninety-eight major complications were recorded.

Twelve deaths were caused by renal lesions and uremia which developed in twelve hours to twelve days after the examination. Renal complications are in direct proportion to the amount of the contrast medium which reaches the kidney. Iopax 75 per cent, hypaque, miokon, and urokon caused fewer complications than when 70 per cent diodrast was used. Pathologically, changes were found in the glomerules and tubules. In particularly severe cases, the entire kidney was found to be diffusely hemorrhagic and necrotic.

Five deaths occurred as the result of neurologic complications. The most frequent were transverse myelitis, paraplegia and flaccid paralysis of the lower extremities below the level of the eighth thoracic segment. Most of the neurologic complications are caused by a toxic reaction of the contrast media upon the medulla and possibly arteriospasm producing medullary ischemia. Neurologic complications increase in proportion to the amount of the contrast medium used, but can occur with as little as 10 cc. of 70 per cent urokon. Apparently, the frequency of neurologic complications is reduced with local anesthesia.

Five patients died as the result of hemorrhage at the site of injection. The bleeding was usually retroperitoneal, perirenal or superficial. In one case, the puncture caused a hemithorax followed by surgical shock. Generally, the bleeding took place at once, but sometimes it was delayed. In 3 cases, hemorrhage was caused by direct puncture of aortic aneurysms; on the other hand, in 25 cases in which aneurysms were penetrated, it did not cause serious hemorrhage.

Thirteen serious cardiovascular reactions were observed. These were generally in patients in poor health or advanced age. In 5 patients, surgical shock occurred a few minutes after the injection. All of these patients survived. Cardiac failure was seen in 3 patients. Only one survived. One patient with a rheumatic mitral affection died of cerebral embolus. In 3 cases, anesthesized with pentothal, an acute coronary occlusion occurred two hours after recuperation from the anesthesia. Two of these patients died. Elevation of the arterial pressure associated with cardiac arrhythmia was an ominous complication. Two deaths were cited as being caused by pheochromocytomas.

Ten gastrointestinal complications were observed. Five of these were fatal following the injection of diodrast or urokon. In 3 cases, the superior mesenteric artery was injected. Two deaths were attributed to gangrene of the intestine. One death was caused by perforation and peritonitis. One case of narrowing of the abdominal aorta was reported in which there was a regurgitation of the iodine solution into the celiac trunk. Autopsy showed a necrosing arteritis with hemorrhagic pancreatitis and hemorrhagic inflammation of the suprarenal glands.

Three deaths were attributed to pentothal anesthesia. Six cases of severe laryngospasm were described; one of these died. One cardiac failure was attributed to anesthesia. Cerebral hemorrhage occurred in one case with recovery after six weeks. One perirenal abscess required surgical drainage and three cases of infection were attributed to the translumbar needle. One death occurred following a dissecting aneurysm of the aorta and renal arteries. Pneumothorax occurred in 4 patients and 3 developed a chylothorax as the result of division of the thoracic duct. Hematomas were found in 5 out of 375 cases where a retrograde femoral sound was used. Abdominal and scrotal skin gangrene developed in a diabetic patient following injection of 70 per cent urokon under local anesthesia. Extension of an arterial thrombus occurs only rarely. In 3 per cent of the cases, the needle caused lesions in the soft tissues outside of the aorta. Some patients suffered diarrhea, while in others instability of the aortic pressure was noted. Urticaria appeared in 2 to 6 per cent of the cases. Extravasation of the medium caused lumbar and epigastric pain of short duration.

It is not possible to avoid all complications resulting from aortography, but they can be reduced by the adoption of precautionary measures. Above all, the technique should not be used unless there is a clear indication.—*Murray M. Friedman, M.D.*

Koszewski, Bohdan J., Reedy, William J., and Iwerson, Frank. Sudden death due to translumbar aortography. *Ann. Int. Med.*, April, 1958, *48*, 902–907. (From: The Departments of Medicine and Orthopedic Surgery, Creighton University School of Medicine and Creighton Memorial St. Joseph's Hospital, Omaha, Neb.)

Aortography was performed on a sixty-eight year old white diabetic male who had clinical evidence of occlusion of the right common iliac artery. The intraocular test to sodium acetrizoate (urokon) was negative and an intravenous injection of 2 cc. of contrast medium showed no untoward reaction. Under local anesthesia, the needle was inserted into the aorta below the 12th rib. Thirty cc. of 70 per cent urokon was injected rapidly. The roentgenograms demonstrated complete obstruction of the right common iliac artery and an appositional thrombus along the wall of the distal aorta. One minute after the injection, the patient became dyspneic and cyanotic, and urticaria appeared. Despite immediate injection of epinephrine, he died in pulmonary edema.

Autopsy revealed a small amount of fluid in the paraaortic tissues in the line of the needle tract, but there was no other unusual reaction locally. There was moderate pulmonary edema. The heart was dilated. The coronary arteries and aorta revealed severe atherosclerosis. There was an area of fibrosis in the anterior wall of the left ventricle and septum. It was concluded that death was due to an allergic reaction in a person with a damaged cardiovascular system.

The authors review the complications incident to aortography and they emphasize that sensitivity reactions cannot be absolutely prevented by previous testing and careful selection of patients. They believe that the use of cortisone as a prophylactic medication is rational, and they now give 100 mg. of cortisone orally four hours prior to aortography.—*John L. Williams, M.D.*

Joos, Howard A., and Johnson, John L. Retrograde aortography under hypothermia in infancy and early childhood. *Am. Heart J.*, May, 1958, *55*, 743–753. (From: The Department of Pediatrics, University of Southern California School of Medicine, and the Children's Hospital, Los Angeles, Calif.)

A method of retrograde aortography for use in infants and young children is described. The procedure is done under general anesthesia and hypothermia, reducing the body temperature to about 32° to 33°C. An ice bath or application of plastic bags filled with ice cubes was used to reduce body temperature. Seventy-five per cent hypaque in doses of 0.75 cc. /kg. to 1.0 cc./kg. body weight was used as the medium injected. The injection was made by manual pressure retrograde into an artery. A biplane Elema roll-film changer was used making 12 roentgenograms the first second after injection and 6 to 12 roentgenograms the second second after injection. No significant complications were encountered in the 27 patients reported.

In all cases visualization of the aorta and other major vessels was good. The procedure is considered especially useful in the diagnosis of coarctation of the aorta, patent ductus arteriosus and aorticopulmonary window. It is useful to differentiate between patent ductus arteriosus or aorticopulmonary window and ventricular septal defect. The hypothermia slows the circulation sufficiently to minimize the dilution of the contrast medium and lengthens the time of opacification so that better roentgenograms may be obtained. The authors believe that the hypothermia enhances the safety of the procedure.—*Frank M. Windrow, M.D.*

Beebe, Richard T., Powers, Samuel R., Jr., and Ginouves, Edward. The early diagnosis of ruptured abdominal aneurysm. *Ann. Int. Med.*, April, 1958, 834–838. (From: The Departments of Medicine and Surgery, Albany Medical College and Albany Hospital, Albany, N.Y.)

The authors state that 18 patients with ruptured abdominal aneurysms were admitted to their hospital in five years, but in only 7 was the diagnosis made in time to permit surgical exploration. In 5 of these patients roentgenograms of the abdomen showed obliteration of the psoas and renal shadows on the side of the hemorrhage. They feel that this sign is of great diagnostic value.

The authors also observed 2 other diagnostic aids: (1) The loss of deep tendon reflexes of the lower extremities; and (2) the presence of ecchymosis on the lower anterior abdominal wall.

Early diagnosis will permit utilization of the remarkable improvements of vascular surgery and lead to a markedly decreased mortality in this disease.—*Arthur E. Childe, M.D.*

Husni, Elias A. A new needle and safer method of arteriography. *Surg., Gynec. & Obst.*, May, 1958, *106*, 627–630. (From: The Department of Surgery, Western Reserve University, at City Hospital of Cleveland, Cleveland, Ohio.)

The more serious complications to lumbar arteriography include intramural injection and extravasa-

tion of contrast material; renal fibrosis and atrophy; bleeding from puncture site; mesenteric artery thrombosis; embolism; paraplegia and radiation hazard to the angiographer. The author describes a new injection needle to combat some of these complications. It is 16 gauge and 17 cm. long. The tip is solid and has a short sharp bevel with a rather large side aperture opposite the bevel. A small projection at the base of the aperture acts as an atomizer and reduces a narrow high pressure stream into a low pressure wide angle spray. It is claimed that extraluminal and intramural injections are obviated, and renal damage due to a high pressure stream is lessened. There is less bleeding from the puncture site.

The author describes his method of arteriography in detail. To effect better protection of the operator from radiation, a 130 cm. plastic tubing is used in the injection technique, the operator standing behind a lead screen completely protected.—*Arch H. Hall, M.D.*

General

Blakemore, William S., Murphy, John J., Pendergrass, Henry P., and Greening, Roy R. Carbon dioxide as contrast medium in roentgenography. *J.A.M.A.*, May 17, 1958, *167*, 310–312. (Address: W. S. Blakemore, University of Pennsylvania School of Medicine, 36th and Spruce Streets, Philadelphia 4, Pa.)

This article re-emphasizes the potential danger of gas embolism when using air or oxygen as roentgenographic contrast media. Whereas the use of carbon dioxide minimizes this danger, its rapid absorption from soft tissues and body cavities may make it difficult to obtain acceptable roentgenograms. The authors report the experience at the University of Pennsylvania in which this rapid disappearance from the retroperitoneal space prevented completely ideal examinations when carbon dioxide was injected by the presacral route. Direct perirenal injections on the other hand were satisfactory and diagnostic roentgenograms could be obtained up to ten or twenty minutes after injection.—*James A. Martin, M.D.*

Pettinari, V., Baccaglini, M., and Castiglioni, G. C. Opacification des formations pathologiques privées de contraste naturel. (Opacification of pathologic formations deprived of natural contrast.) *J. de radiol., d'électrol. et de méd. nucléaire*, March–April, 1958, *39*, 117–123. (From: The Institute of Surgical Pathology of the University of Padua, Padua, Italy.)

This is an experimental study of contrast injection of pathologic formations deprived of natural contrast. The method consists of an exploratory puncture with a thin needle of the abnormal formation, which may be deep or superficial. If the needle is not in a vascular lumen, and after possible aspiration of pathologic fluid, radiopaque water-soluble material is injected with a connecting syringe. The quantity of the contrast substance varies with the extent of the lesion to be studied and the ease of the injection. In general, a small amount (1 to 3 cc.) is sufficient. Then serial roentgenograms are taken at thirty seconds, one, two, five, eight, ten, and twenty minutes.

With this procedure, a study of the pathologic formation is made possible by analyzing the distribution and absorption of the radiopaque material. Other anatomic informations are obtained on the form of the virtual cavity, its limits, its internal structures, the vascular and lymphatic drainage and the intactness and permeability of the capsule.

The technique has been used in studying the following particular conditions: sebaceous cyst of the scalp, facial congenital cyst, nodular formation in a goiter, localized cystic mastosis, sarcomatous cystic involvement of a clavicle, funicular cyst, inguinal hernial sac, etc.—*H. P. Lévesque, M.D.*

Gould, David M., and Daves, Marvin L. A review of roentgen findings in systemic lupus erythematosus (SLE). *Am. J. M. Sc.*, May, 1958, *235*, 596–610. (From: University of Arkansas Medical Center, Little Rock, Ark., and National Institutes of Health, Bethesda, Md.)

This article reviews the historical landmarks, the clinical manifestations, and the laboratory and roentgen findings in systemic lupus erythematosus. The most common roentgen manifestation is evidence of pleuritis. The pleural reaction is often minimal and bilateral. Massive effusions are infrequent. The fluid is fibrinous and does not usually move with a change in position of the patient.

Pneumonitis occurs in approximately 50 per cent of patients. The most common appearance is that of ill-defined patchy densities at one or both lung bases. The lesions resemble infarctions or bronchopneumonia and they often wax and wane on successive studies. In chronic cases horizontal atelectatic plaques may occur.

Carditis is present in 53 per cent of patients. The size and configuration of the heart may vary markedly within a period of days or weeks. Although a pericarditis is often present, the amount of fluid is usually scanty and the increase in heart size appears to be due primarily to a myocarditis, rather than to pericardial effusion.

Gastrointestinal and abdominal symptoms are very common but roentgenographic abnormalities tend to be rather subtle. Barium studies generally reveal lack of tone, slight dilatation, and poor peristaltic activity. The abnormalities are similar to those found in scleroderma, but are much milder in

degree. Splenitis with slight enlargement of the spleen is said to occur in 34 per cent of patients.

Severe arthralgia is common in systemic lupus erythematosus, but the roentgenograms are normal or show only minimal nonspecific changes similar to those of early rheumatoid arthritis. Even in the chronic form of the disease there is usually no evidence of destructive changes in the cartilage or the bone.

The roentgen findings in systemic lupus erythematosus are individually ill-defined and nonspecific, but collectively they form a well-defined pattern.—*John L. Williams, M.D.*

Riebel, Frank A. Use of the eyes in x-ray diagnosis. *Radiology*, Feb., 1958, *70*, 252–258. (Address: 15 W. Goodale St., Columbus 8, Ohio.)

The author presents certain practical suggestions for systematic study of roentgenograms. A fixed routine is recommended for scanning roentgenograms so that no details are overlooked. Adherence to a definite roentgenographic study plan and constant practice to expand the visual fields are essential. The efficiency of the first quick survey of a roentgenogram is enhanced, if the operator, by practice or formal training, expands his visual fields to comprehend more territory at a glance or on successive fixations.

Complete dark adaptation is essential for fluoroscopy. Red goggles can never produce the dark-adapted eye, but adaptation proceeds more rapidly after the use of red goggles. On an average, four minutes are required in complete darkness after red goggles have been worn for twenty minutes before the eyes are ready to view thick parts. Dark adaptation is lost rapidly on exposure to bright light and there is considerable loss by looking at roentgenograms even through red goggles. Peripheral vision should be used habitually (excepting only the study of rapid motion) and will contribute much to what can be seen.—*Arno W. Sommer, M.D.*

Shapiro, Jerome H., and Jacobson, Harold G. File room operation in a radiology department. *Radiology*, Jan., 1958, *70*, 87–89. (Address: J. H. Shapiro, 210th St. and Bainbridge Ave., New York 67, N.Y.)

The authors describe a combination of vertical sorting and vertical distribution tabulating systems in the operation of the file room in the radiologic department of a large general hospital. The combination of these systems has materially improved the service offered for both the clinicians and the radiologists. Operation of the combined procedures is described in detail.—*Arno W. Sommer, M.D.*

RADIATION THERAPY

Gauwerky, Friedrich. Erfahrungen mit der Verwendung von Caesium[137] bei der intrakavitären Curietherapie gynäkologischer Karzinome. (Experiences in the intracavitary therapy of gynecologic carcinoma with cesium 137.) *Strahlentherapie*, Jan., 1958, *105*, 107–118. (From: Therapeutisches Strahleninstitut des Allgemeinen Krankenhauses St. Georg, Hamburg, Germany.)

Cesium 137 (barium 137) yields a gamma beam with an energy equivalent to 0.662 mev. This monochromatic gamma beam is of "intermediate" hardness, has a half-value layer in tungsten of 3.9 mm., and is reduced to about one third of its intensity by 6 mm. of tungsten. For intracavitary therapy the ability to decrease the intensity of the radiation considerably with relatively thin protective filtration is advantageous.

The author has adapted external radiation, radium therapy and selectively shielded cesium 137 therapy to the needs of 16 patients with carcinoma of the uterine cervix. The chief gain in dosage distribution has resulted from being able to shield bladder, rectum, etc. selectively from intravaginally placed cesium 137 with blocks of tungsten, and thus attain higher doses laterally while sparing chosen tissues from such high doses. He has designed an intravaginal assembly of tungsten blocks which can be varied to suit the individual patient's radiation therapeutic needs.

Neither duration of follow-up nor number of patients treated permits sound conclusions, but physical measurements and calculations show advantages in the addition of cesium 137 and tungsten shields to the therapeutic tools for intravaginal application.—*Henry G. Moehring, M.D.*

Brandt, Hans-Jurgen, and Schlungbaum' Werner. Die endobronchiale Bestrahlung des Bronchuskarzinoms. (Endobronchial irradiation of bronchial carcinoma.) *Strahlentherapie*, Feb., 1958, *105*, 207–217. (From Landestuberkulose-Krankenhaus Heckeshorn und Strahleninstitut der Freien Universität Berlin am Städt. Krankenhaus Westend, Berlin, Germany.)

As a complement to surgical and external radiation methods of treating bronchial carcinoma, the authors have used a combination of modern anesthesia and repeated one to four endobronchial applications of cobalt 60 pearls strung on a semiflexible wire.

Indications for thus complementing more conventional therapy were: (1) Inoperability because of systemic or local conditions; (2) contraindications to external radiation therapy; *e.g.*, general condition of the patient; (3) endobronchial tumors with stenosis of large bronchi; (4) tumor residuals in postoperative bronchial stumps; and (5) superficial tumors extending in the bronchial mucosa to the trachea.

The maximum dose attained in a single four-hour

sitting was 4,000 r. Sittings numbered from several to six. Although palliation was the aim in managing their patients, the authors report one patient who died eight months after such endobronchial therapy (of pulmonary embolus after resection of a bladder tumor); extensive examination of the bronchial tree showed no evidence of residual tumor.

The most gratifying results have been obtained in those patients whose tumors were occluding a bronchus and causing distal atelectasis and pneumonitis.—*Henry G. Moehring, M.D.*

Garland, L. Henry. The treatment of cancer of the breast. The Carman lecture. *Radiology*, Feb., 1958, *70*, 159–190. (Address: 450 Sutter St., San Francisco 8, Calif.)

A comprehensive discussion of carcinoma of the breast is presented, based on reports in the literature, government statistics and personal experience of the author.

The preclinical phase of mammary cancer appears to be relatively long and the clinical phase is usually manifest for several months before the average patient presents herself for treatment. Most patients have tumors over 20 mm. in diameter when first detected; very rarely one is diagnosed when it is still only a few millimeters in size. The duration from first symptoms to diagnosis is reported to average about one year. Metastases may already have occurred when the diagnosis is made. The malignancy of breast cancer varies widely. The histopathologic type or grade of the tumor has considerable bearing on the clinical behavior, the prognosis and the radiosensitivity. More important is the "growth potential" and the clinical extent or stage of disease at the time of treatment. Location of the primary tumor probably does not influence prognosis greatly.

Spread of breast cancer occurs by numerous routes. Lymphatic spread occurs via many pathways, including the subareolar and subcutaneous lymphatic channels, the main axillary trunks, the pectoral group and the internal mammary chain. Vascular spread occurs through the mammary veins to the axillary and supraclavicular veins, through the internal mammary veins and through the intercostal veins. Direct extension occurs through the tissue spaces in the breast and the muscles of the chest wall.

The author concludes that, in general, Stage I to III cases should be treated by simple mastectomy and radical postoperative roentgen therapy. Selected cases may be treated by radical mastectomy or by roentgen therapy alone. Most Stage IV cases should be treated by roentgen therapy or hormone therapy.

Various treatment programs, including the McWhirter method, are discussed. The author's treatment technique is described in detail. A midshoulder lymph node dose of about 4,000 rads and a midchest wall dose of about 3,700 rads are delivered in four weeks. He has treated a total of 62 patients with primary carcinoma of the breast by vigorous roentgen therapy following simple mastectomy. An analysis of his results and a comparison with results reported by other authors are presented.—*Arno W. Sommer, M.D.*

Dargent, M., Papillon, J., Montbaron, J. F., and Costaz, R. Étude urographique du cancer du col utérin traité par l'association radium-lymphadénectomie. (Urographic study of cancer of the uterine cervix treated by an association of radium and lymphadenectomy.) *J. de radiol., d'électrol. et de méd. nucléaire*, March–April, 1958, *39*, 109–116. (From Centre Professeur-L.-Bérard, Lyon, France.)

This is a urographic study based on more than 400 patients who were treated for carcinoma of the cervix, Stage I and II, by a combination of irradiation, mostly radium, and surgery.

Intravenous pyelography was done systematically before radium insertion; before operation; about fifteen days after operation; and thereafter at regular intervals of three to six months for three years. The present analysis concerns only 55 cases who had this systematic examination carried out over a long enough period to be clinically significant.

The radium therapy was administered in 2 steps: vaginal and intrauterine insertion. Doses ranged from 30 to 77 mc destroyed, with an average of 57.6 mc destroyed. There was no relationship between high radiation dosage and urinary tract complications. The complications that appeared were manifested early and were encountered in the low dosage group. Further aggravation was caused by pelvic recurrence of the carcinoma.

The surgery was carried out from six to eight weeks after irradiation. It consisted of the removal of the iliopelvic lymph nodes, accompanied by either simple hysterectomy or by a wider procedure, such as Wertheim's or Brunschwig's operations.

As a result of these studies, it was found that: (1) ureterohydronephrosis observed preoperatively was caused by rapid carcinomatous invasion and was noted in 3 cases; (2) early postoperative urographic abnormalities (which appeared in 52 per cent of the cases) occurred more frequently in the group of patients who had extensive surgery as compared with those who had simple hysterectomy; (3) follow-up urographic studies revealed spontaneous return to normal pyelogram in 60 per cent of the patients who had postoperative hydronephrosis, irrespective of the surgical procedure. These transient changes were attributable to postoperative dyskinesia resulting from ureteral dissection or in a few cases possibly to hypokalemia; (4) progressive and irreversible pyeloureteral dilatations were seen in only 2 patients out of the 18 who had simple hysterectomy and in 12 patients out of 34 who had more extensive surgery. In

the 2 patients of the former group and in 6 patients of the latter group, the changes were attributable to peri-ureteral sclerosis, which is particularly prone to occur in patients who have had a dissection of the terminal ureter such as in a Wertheim or a Brunschwig procedure; and (5) another complication, besides hydronephrosis, was pyelonephritis which was encountered in 14 cases, in 4 after simple hysterectomy and in 10 after Wertheim's operation. Of this latter group, 7 became normal subsequently and 3 were aggravated by neoplastic recurrence.

Bladder incontinence occurred in 8 cases due to neuromotor disturbance after Wertheim's operation. In 2 of these, it was caused by pelvic carcinomatous infiltration, and in 2 others by sclerosis.

Fistula of the terminal ureter was noted in 7 cases. One dried up spontaneously without urographic changes. Three were the result of carcinomatous involvement. The remaining three were accompanied by hydronephrosis that gradually cleared with the drying up of the fistula, except one which resulted in a homolateral silent kidney and contralateral hydronephrosis.

In conclusion, the authors emphasize the prognostic significance of an altered pyelogram in the initial evaluation of a cervical carcinoma. Intravenous pyelography should be done routinely to ascertain the clinical stage of the disease. From the surgical point of view lymph node removal accompanied by simple hysterectomy should be recommended instead of Wertheim's operation, to avoid urinary tract complications attributable to dissection of the distal ureter. The removal of cellulous fascia of the uterine artery in Wertheim's operation plus the latero-vesical fascia in Brunschwig's operation seems superfluous, if one considers the sterilizing effect of irradiation; moreover, it should be avoided if one has in mind the ureteral complications.

Finally, any surgical intervention intended to correct a ureteral stricture, associated with a fistula or hydronephrosis, should be decided upon with caution in view of the transient and reversible character of many of these complications. If a surgical correction is contemplated, an ileocystoplasty is preferable to nephrectomy in the conditions discussed above.—*H. P. Lévesque, M.D.*

Gray, Mary Jane, Plentl, Albert A., and Taylor, Howard C., Jr. The lymphocyst: a complication of pelvic lymph node dissections. *Am. J. Obst. & Gynec.*, May, 1958, *75*, 1059–1062. (From: The Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, the Sloane Hospital for Women, and the Francis Delafield Hospital, New York, N. Y.)

The term lymphocyst is used to designate the pathologic accumulations of fluid in the region of the great vessels of the pelvis, a troublesome complication of pelvic lymphadenectomy. This cyst usually develops over a period of one to six months postoperatively.

Since 1952, 55 pelvic lymphadenectomies have been performed at the Sloane Hospital for Women and the Frances Delafield Hospital in patients previously treated with radium and external roentgen therapy for carcinoma of the cervix. This is the first report concerning lymphocysts to appear in American literature. The diagnosis of lymphocyst was made in 9 instances, 8 times clinically and once from autopsy findings.

There was no significant correlation between increasingly radical dissection and the incidence of lymphocyst as noted by other investigators. The number of lymph nodes removed was insignificantly higher in those patients developing a lymphocyst. The lack of control patients renders the influence of radiation obscure. Alteration of operative technique from extraperitoneal to the transperitoneal approach increased the relative incidence of this complication. Routine incisional drainage increased the incidence of lymphocyst from 12.5 per cent to 28.5 per cent.

This complication, developing as a result of lymphadenectomy, following primary radiation therapy, was responsible for the death of one patient and an additional operative procedure in 6 patients in this series. Since it is probable that several cases escaped detection during follow-up, the true incidence of lymphocyst was probably greater than the observed rate.

The inability to prevent the formation of lymphocysts under these conditions has made it advisable to abandon pelvic lymphadenectomy as a routine procedure after radiation therapy for carcinoma of the cervix.—*James J. Snider, M.D.*

Baily, Norman A., and Beyer, Norman S. Exit dosage for 2-MVP x-rays. *Radiology*, March, 1958, *70*, 395–397. (From: Roswell Park Memorial Institute, Buffalo 3, N. Y.)

In the use of supervoltage roentgen rays, it has been shown that the surface dose through the entrance portal is considerably lower than the peak dose. In many cases, the dose to the skin covered by the exit port will exceed that delivered to the skin comprising the entrance port. It is, therefore, of importance to know the deviation of the exit dose from that read from depth-dose curves as measured in infinite phantoms.

A comparison of percentage depth dose obtained at various depths in an infinite phantom using a thimble chamber and a large field extrapolation chamber is made for one field size (10×10 cm.). The experimental results of exit dose measurements made with the large field extrapolation chamber for field sizes ranging between 25 and 625 cm.^{2} are presented, expressed both as percentage of the peak dose and deviation from the values of the center-line

depth doses measured in an infinite water phantom. —*Walter H. Jarvis, Jr., M.D.*

Pilheu, Federico R. Branquiomas, a propósito de 30 observaciones. (Branchiogenic cysts; a report of 30 cases.) *Prensa méd. argent.*, Nov. 15, 1957, *44*, 3350–3363. (Address: Soler 3388, Buenos Aires, Argentina.)

Thirty patients with branchiogenic cysts were studied. Of these, 17 were in males and 13 in females. The greatest incidence occurred in the age groups of twenty and forty years. In 10 patients, the tumors developed within one year. In 19 patients, development was within three years. In one case, aged sixteen, the tumor developed over a period of ten years. The lesion was complicated by the presence of bilateral branchiogenic fistulas, which were present since birth. The most frequent symptom was the presence of a tumor which had existed six, eight, ten months or more. The tumor did not change in size and caused no symptoms. Symptomatically, the tumors are characteristically situated in the neck anterior to the sternocleidomastoid muscle. In the series presented, none showed evidence of malignant change.

The etiology of branchiogenic cysts is discussed. The authors favor the theory of a defect in the involution of the embryologic "cervical chest."

All 30 cases were treated surgically. In all but one case, local anesthesia was used.—*Murray M. Friedman, M.D.*

RADIOISOTOPES

Rosenberg, Gilbert. Biologic half-life of I^{131} in the thyroid of healthy males. *J. Clin. Endocrinol. & Metab.*, May, 1958, *18*, 516–521. (From: Senneville Geriatric Research Unit, Ste. Anne's Hospital, Ste. Anne de Bellevue, Quebec, Canada.)

Having previously established that there is a progressive decrease in the twenty-four hour percentage uptake of I^{131} by the thyroid gland with advancing age, the author sought further understanding of thyroid function in old age by measuring the biologic half-life of thyroidal I^{131} in 38 healthy, clinically euthyroid males ranging in age from twenty-two to eighty-three years.

The thyroidal uptake of the oral tracer dose of 50 μc of I^{131} was measured in a conventional manner and the data plotted semilogarithmically. Biologic half-life was taken as the day on which half of the theoretical twenty-four hour percentage uptake was still present in the neck. It ranged from a low of twenty-one days to a high of two hundred days.

In subjects fifty years of age and over, the biologic half-life of thyroidal I^{131} appeared directly proportional to age and inversely proportional to the initial twenty-four hour percentage uptake. In subjects less than fifty years of age, the biologic half-life was more or less independent of the age of the subject and of the twenty-four hour percentage uptake of I^{131}.

The author feels that variation in the re-accumulation of I^{131} may explain this difference between young and old subjects. He concludes that the results are compatible with the concept of a progressive decrease in secretion of thyroid hormone due to decreased peripheral utilization with advancing age.—*Donald M. Monson, M.D.*

Schultz, Alvin L., and Zieve, Leslie. Relationships between clinical severity of hyperthyroidism and results of thyroid function tests. *J. Clin. Endocrinol. & Metabol.*, June, 1958, *18*, 629–635. (From: The Department of Medicine and Radioisotope Service, Veterans Administration Hospital and University of Minnesota, Minneapolis, Minn.)

In an attempt to develop a practical means of grading the clinical severity of hyperthyroidism, and to relate this index of clinical severity to the results of thyroid function tests, a quantitative clinical severity score was derived by rating the most important symptoms and signs of hyperthyroidism on a seven-point scale, weighting the items on the basis of their clinical importance, and combining the weighted ratings to get a single score.

Groupings of 5 major clinical variables entered into the severity score: (1) Hyperactivity and tremor; (2) heat intolerance and excessive sweating; (3) tachycardia at rest; (4) weight loss; and (5) a miscellaneous group which included increased appetite or number of stools (3 or more per day), persistent fever, weakness, silky skin and fine hair, stare and lid lag, increased pulse pressure (over 50 mm. Hg), and increased nervousness or emotional lability. The ratings of the first 2 groupings were weighted at 1.5, and the others at unity.

In 53 patients with unequivocal clinical hyperthyroidism, correlations between the clinical severity score and 9 test variables ranged from 0.15 to 0.61. The highest correlations of clinical severity were with the thyroidal clearance of I^{131} (0.61), the three hour thyroidal I^{131} uptake (0.59), the rate of uptake of I^{131} dose by the gland (0.57), and the basal metabolic rate (0.44). Correlations with the chemically determined serum protein-bound iodine level, twenty-four hour thyroidal I^{131} uptake, serum cholesterol level, serum protein-bound I^{131} level and conversion ratio were 0.30 or less in decreasing order.

The best linear combination of all nine tests for purposes of predicting clinical severity raised the correlation to only 0.74. Two tests alone, the thyroidal I^{131} clearance and the basal metabolic rate, were as effective as all tests together for use in predicting clinical severity, yielding a multiple correlation of 0.72.

All this still, however, leaves 45 per cent of the

variation in the predicted (clinical) variable unaccounted for by the results of the tests. The authors, therefore, conclude that these functional tests are relatively inexact bases for comparing patients as to severity of hyperthyroidism. They feel that clinical appraisal remains the best means of comparing severity among individuals or groups, and that the clinical severity score which they discuss is a convenient objective measure to use for this purpose.—*Donald M. Monson, M.D.*

Bolinger, Robert E., and Grady, Harold J. The plasma insulin—I^{131} in diabetic patients. *Ann. Int. Med.*, April, 1958, *48*, 753–764. (From: The Department of Medicine, University of Kansas School of Medicine, Kansas City, Kans.)

This study presents data obtained concerning the disappearance of I^{131}-labeled insulin from the plasma in normal and diabetic subjects. The possibility that none of the relatively small number of labeled molecules retains insulin effect must be borne in mind.

Insulin was labeled by direct iodination. The studies were conducted on fasting patients who had received no insulin for the previous twenty-four hours. Each patient received an intravenous injection of 3.0 units of the labeled insulin per $m.^2$ of body surface. Blood samples were taken at intervals of ten to twenty minutes for the succeeding one to two hours. Assay of blood samples was carried out with an end-window Geiger counter.

Twenty patients were divided into 4 categories. Group I, normals; Group II, obese diabetics not dependent on insulin; Group III, diabetics with the onset of disease between the ages of twenty and forty, dependent on insulin for weight maintenance and no history of acidosis; Group IV, diabetics dependent upon insulin for weight maintenance, with history of acidosis and the onset of disease in adolescence or childhood.

In man the plasma disappearance curve for labeled insulin consists of an initial rapid phase followed by a slower second phase. This curve was found for all diabetic groups. The initial phase is completed in fifteen minutes after injection. Comparison of the slope of the initial phase disappearance with that of the second phase reveals the former to be significantly faster.

The second phase of labeled insulin disappearance followed a first order relationship such that:

$$\text{Log } Y = A + B_2X$$

where Y is the serum concentration of labeled insulin expressed in micro units per ml. and X is the time after injection in minutes. The constant A represents the extrapolated logarithmic value of the labeled insulin curve at zero time, and B_2 is the rate constant characteristic of the insulin disappearance during the slow second phase.

The values for the latter constant vary widely within the normal group. There is no significant difference between the normals and the abnormals. Therefore, it is no characteristic for any diabetic group. The values for A are significantly lower for Group II than any of the other groups. The significant negative correlation exists in Groups I and III between the value for these two constants (A and B_2). No correlation is noted between blood sugar decline rates and either of the two constants A or B_2.

Four factors may be considered important in determining the characteristic of the disappearance curve of labeled plasma insulin. The size of the endogenous insulin pool must be known, theoretically, to assign a specific activity to the tracer. Knowledge of the latter is essential to determining the disappearance constant for the labeled insulin. Changes in endogenous pool size can effect varying values for the disappearance constant. These alterations are significant, and this is one factor contributing to the great variation in results. Plasma binding of insulin has been described with the suggestion that saturation of the binding mechanism may partially determine this activity. The values for the slow phase of disappearance constant will change commensurately. Cellular binding of insulin is probably reflected in the initial rapid phase of the disappearance of labeled insulin from the plasma, and tissue degradation may also influence the initial phase of disappearance of labeled insulin from the plasma.

There is poor correlation between clinical classes of diabetes and alterations in the disappearance characteristics of labeled insulin. The size of the endogenous pool is indeterminable, but can effect the disappearance rate of labeled insulin. Caution must be exercised in applying the findings obtained from labeled insulin studies to an interpretation of the clinical status of the diabetes.—*James J. Snider, M.D.*

Seal, S. H., Crosignani, S., Valvassori, G., Nickson, J. J., and Agostino, D. The treatment of malignant effusions with radioactive colloidal gold (Au^{198}); a review of sixty-six cases. *Am. J. Obst. & Gynec.*, May, 1958, *75*, 1027–1033. (From: Memorial Center for Cancer and Allied Diseases, Sloan-Kettering Institute for Cancer Research, and Cornell University Medical College, New York, N.Y.)

Muller initially employed intraperitoneal radioactive colloidal gold in the treatment of ascites due to peritoneal carcinomatosis. Pursuant studies demonstrated favorable results in 30 to 40 per cent of patients with malignant effusions receiving similar therapy.

The results of four years' experience with the intracavitary administration of radioactive colloidal gold at the Memorial Center for Cancer and Allied Dis-

eases are presented. Therapeutic doses of Au^{198} were administered to 111 patients with malignant growths involving the pleural and peritoneal cavities. Thirty-two cases were lost to follow-up. Eight patients expired within one month of treatment. Five patients were treated prophylactically. These were excluded from the study. The remaining 66 patients displayed effusions of proved malignant etiology. Their most important symptoms were incident to fluid re-accumulation, requiring frequent taps. Single intrapleural doses ranged from 75 to 110 mc, averaging 85 mc. Intraperitoneal doses varied from 150 to 225 mc. The usual amount employed was 175 mc. The instillation technique of Rose was utilized, and no complications were noted.

"Good palliation" was achieved when no taps were required for a period of two months after treatment. "Fair palliation" was realized when taps were required within a period of one to two months after treatment. "No palliation" was recorded when a tap was required less than one month after treatment and fluid re-accumulated in less than two months.

Thirty-four patients were treated intrapleurally. Of these, 47 per cent had lung tumors; 17.6 per cent had ovarian tumors; 11.7 per cent had breast tumors; and 11.7 per cent had lymphomas. Good palliation was achieved in 23 patients; fair palliation in 7 patients; and no palliation in 4 patients.

Thirty-two patients were treated intraperitoneally. Sixty-two per cent of these had ovarian tumors, and 21 per cent had tumors of the colon. Good palliation was achieved in 19 patients; fair palliation in 7 patients; and no palliation in 6 patients.

Many of these patients received combined therapy utilizing combinations of roentgen, isotope, and chemotherapy. Evaluation of results in these instances was difficult.

In this study of 66 patients treated with intracavitary radioactive colloidal gold, the authors observed good palliation in 63.6 per cent; moderate palliation in 21.2 per cent; and no palliation in 15.1 per cent. Additionally, these observers state that 70 per cent of the patients experienced relief of subjective symptoms. There is no correlation between survival time and administration of Au^{198}.—*James J. Snider, M.D.*

Kelly, William A., Evans, Joseph P., Harper, Paul V., and Humphreys, Eleanor M. The effect upon hypophysis of radioactive yttrium. *Surg., Gynec. & Obst.*, May, 1958, *105*, 600–604. (From: The Division of Neurological Surgery, the Argonne Cancer Research Hospital, and the Department of Pathology, The University of Chicago, Chicago, Ill.)

In recent years hypophysectomy has been used in an attempt to control advanced metastatic disease from various sites, but long term effects have been poor and surgical morbidity and mortality have been significant. Autopsies often reveal fragments of residual pituitary tissue.

A more successful technique of ablation using radioactive yttrium 90 pellets was described by Rasmussen in 1953 and subsequently modified by the present authors. Approximately 12 mc of the isotope are divided among 16 sources and placed operatively within the gland. This produces coalescent necrosis with a sharp border formed by a fibrous pseudocapsule, and the degenerative process continues for about two months. The tissue peripheral to the capsule shows chronic alteration, characterized by shrunken cells with small nuclei and clumped chromatin. The functional status of this altered tissue is still unknown.

In 19 autopsy specimens of this series, no case has shown 100 per cent destruction of pituitary, and it was assumed that complete destruction was not obtained in the 24 others still living. However, good evidence of stabilization or healing of metastatic lesions was found in 8 cases. This suggests either that residual viable tissue has altered or arrested function, or that a beneficial clinical response may be seen when only a reduced pituitary function is achieved. —*Arch H. Hall, M.D.*

Fergusson, J. D. Implantation of radioactive material into the pituitary for the control of prostatic cancer. *Brit. J. Urol.*, Sept., 1957, *29*, 215–221.

Radioactive yttrium (Y^{90}) in the form of short rods (usually 2) having an average activity of 4 mc was implanted beside the pituitary gland through needles introduced intranasally. Positional control was obtained by 2 image amplifiers mounted at right angles to one another. Selected cases of carcinoma were chosen wherein castration and estrogen treatment had failed, and also adrenalectomy in some cases. This further method of endocrine control produced no cures or arrest of the disease in the series of 30 cases, but relief from metastatic pain occurred in the majority, and other evidences of regression appeared in a few instances. Partial radionecrosis of the pituitary has been demonstrated histologically.—*Frank A. Riebel, M.D.*

Braestrup, Carl B., and Mooney, Richard T. Cobalt-60 radiation measurements. *Radiology*, April, 1958, *70*, 516–522. (Address: C. B. Braestrup, 99 Fort Washington Ave., New York 32, N. Y.)

The use of cobalt 60 teletherapy equipment presents certain problems not encountered with conventional roentgen therapy apparatus. This is due to the higher energy of the gamma rays and the fact that they are emitted continuously from a source material of significant dimensions. As these factors affect the measurements of the radiation in various ways, it is desirable that certain standard

procedures be adopted in order to permit duplication of techniques between various teletheraphy centers. The results of a study of these factors and procedures are reported and discussed in this paper.

Condenser ionization chambers used to obtain the air exposure dose must have thicker walls in order to secure electronic equilibrium. They must be calibrated specifically for those higher energy rays because of the difference in wavelength dependence of the material used in their construction. Variation in sensitivity of these chambers with different field sizes was found due to chamber stem leakage. This variation limits the practical usefulness of the 100- and 250-r chambers for measuring high energy radiation. Beam control is achieved by use of either a movable shutter or a movable source with the first type of control probably being the better type. Source distance should be measured from the point of interest to the nearest point on the source as that point is usually most easily defined, besides remaining fixed, irrespective of source height.

Definition of true field size is difficult as the source is not a point. With the use of a geometric field, however, this is not a serious objection as the dose distribution in the patient should be determined by the complete isodose pattern for the particular technique used. The air exposure rate should, for clinical purposes, be determined for the distance and field size of interest. Field size should preferably be 100 sq. cm. at the distance of measurements. In cobalt 60 teletherapy as in other forms of supervoltage therapy accurate determination of the depth dose is of great importance since the dose to critical organs near the tumor usually is the limiting factor.—*Donald N. Dysart, M.D.*

MISCELLANEOUS

Soule, A. Bradley, Jr., Heilbronn, Hans, and Bannister, Ralph. The rational use of x-ray in medicine and dentistry with particular regard to protective measures. *J. Maine M. A.*, April, 1958, *49*, 125–134. (From: Department of Radiology, University of Vermont College of Medicine, Mary Fletcher Hospital, Burlington, Vt.)

Recognition of the biologic hazards of radiation, whether from natural background, atomic explosion with consequent fall-out, or peaceful uses of atomic energy from a roentgen-ray machine, has led to the establishment of a maximum permissible dose of radiation for an individual, and this has been calculated for total accumulated dose, permissible rate of increment annually, emergency dose, and weekly and annual dose for exposed personnel. Necessary medical and dental radiation should not be included in this computation.

It is the responsibility of the attending physician and radiologist to keep medical and dental radiation exposure at a minimum consistent with maintenance of health in the individual. In case of doubt concerning the wisdom and safety of an examination involving the use of roentgen rays, it is recommended that the referring physician consult with a radiologist before ordering or performing the examination.

The principles to be followed in order to avoid all unnecessary exposure and minimize the radiation to both the patient and personnel in necessary examinations are listed. These include not only those applicable to equipment and technical factors, but also the shielding of the portion of the patient's body not being studied, particularly the gonads, the shielding of personnel, and the use of monitoring devices.

Specific recommendations concerning the use of roentgenographic examinations during pregnancy are made. In order to avoid irradiating an early embryo in its most vulnerable stage, elective study involving the pelvis of women in the child-bearing age is done only during the first two weeks of the menstrual cycle. Pelvimetric examinations are done with greatest safety in the last month of pregnancy, and a method of examination is described which, by shielding and coning, protects the fetal gonads in those patients in whom the fetus is in a cephalic presentation.

Although survey roentgenograms of the chest by photofluorographic techniques result in thirty times as much radiation to the gonads as a conventional examination performed even without shielding (with shielding there is essentially no radiation to gonads), it is deemed probable that six month survey examinations of the chest offer no appreciable hazard, and controlled mass surveys offer information sufficiently significant to more than balance a probably nonexistent "hazard."

Specific recommendations are made for dental examinations. With use of proper protective devices, shielding, fast film, etc., the radiation involved can be reduced to a value which presents little or no hazard to the patient. Nevertheless, restriction of the use of "routine" full mouth dental examinations, particularly in children, is advised.

The treatment of malignant disease with radiation is not considered in this paper, but the possible leukemogenic effect from radiation for benign lesions is mentioned. Therapeutic use of I^{131} for hyperthyroidism delivers an appreciable dose to the gonads, but the diagnostic use of I^{131} offers no radiation hazard.—*Lois Cowan Collins, M.D.*

Richards, Albert G. Secondary radiation and the dentist. *J. Am. Dent. A.*, July, 1958, *57*, 31–38. (From: School of Dentistry, University of Michigan, Ann Arbor, Mich.)

In operating a dental roentgenographic machine the principal radiation hazard to the dentist is from scatter radiation. He may achieve adequate protection from the primary beam by avoiding its path and by using a machine in which the head has been

built to keep leakage radiation below the recommended limits, but the secondary radiation, extending in every direction from the patient's head, cannot be so easily avoided. Experimentally, using a human skull filled and coated with wax and a dental machine, the quantity of scatter radiation was measured to determine the amount of secondary radiation delivered in relation to distance and direction from the patient's head, and kilovoltage used.

Values are tabulated, showing that the safest position for the operation of a dental roentgenographic machine is behind the patient's head, and that the quantity of secondary radiation decreases with distance. The secondary radiation increases with increase in kilovoltage. However, when this is compensated by the lesser quantity of exposure (mas.) required, the resultant secondary radiation is the same except in a few locations, such as behind the patient's head, in which location the higher kilovoltage would deliver a slightly greater quantity of secondary radiation in spite of the exposure corrections.

Permissible workloads calculated in the number of one second exposures per day which will result in a quantity of secondary radiation within the recommended .100 r per week limit are tabulated for the different positions in relation to the patient's head. A sufficiently large factor of safety is allowed to compensate for the slightly increased secondary radiation when 90 kv. is used in certain locations.—*Lois Cowan Collins, M.D.*

Looney, William B. Effects of radium in man. *Science*, March 21, 1958, *127*, 630–633. (From: The Department of Radiotherapeutics., University of Cambridge, Cambridge, England.)

It seems advisable to lower the MPC (maximum permissible concentration) for such radioactive elements as strontium, plutonium and radium, at least until information becomes available on the effects of radium in man over a normal lifetime.

The present MPC of .1 microgram was established by the United States Bureau of Standards in 1941 based on individuals who had carried radium in their bodies for periods varying from seven to twenty-five years. Seven individuals carrying .02 to .5 micrograms had no observed changes referable to the radioactive material, but death occurred in patients having as little as 1.2 micrograms.

Subsequent investigations, having allowed a longer period of time, have shown roentgenographic skeletal changes occurring with .4 micrograms; major skeletal damage at .7 micrograms; and bone tumors at .8 micrograms. Although it has not yet been necessary to change the MPC, the present data are still based on radium carried for less than a normal life span (data accumulated over 34 years), and it therefore seems likely that, when the results are extrapolated over a normal lifetime, "appreciable bodily damage" may occur at or below the present MPC of .1 microgram.

Appreciable bodily injury is defined as "any bodily injury that a person would regard as objectionable and/or competent medical authorities would regard as being deleterious to health and well being of the individual." This may be interpreted as (1) microscopic skeletal change, (2) roentgenographic skeletal change, (3) major clinical damage, and (4) neoplasia. From the extrapolation of results from the patients under observation, both microscopic and roentgenographic evidence of bone damage may be expected from .1 microgram of radium over a normal lifetime. Major skeletal changes may be expected to occur in old age of patients who have carried the MPC for a normal lifetime, because of the combination of effects of increasing accumulated dose, decreasing ability of the body to repair skeletal damage, and atrophy of the skeleton in old age. Extrapolation of the results of bone tumor induction from radiation beyond forty years in man is difficult, and more work must be done before it will be possible to discuss with any confidence the mechanism of radiation carcinogenesis, or MPC of radium in relation to it.—*Lois Cowan Collins, M.D.*

Porter, K. A., and Murray, J. E. Long-term study of x-irradiated rabbits with bone-marrow homotransplants. *J. Nat. Cancer Inst.*, Jan., 1958, *20*, 189–206. (From: Laboratories for Surgical Research, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.)

The authors exposed male New Zealand white rabbits to 1,100 r whole-body x-irradiation fractionated into 2 doses; an initial dose of 600 r was followed twenty four hours later by an additional 500 r. They were then injected intravenously with homologous bone marrow from a female donor and treated with tetracycline hydrochloride for three weeks.

In 65 per cent of the animals, persistence and function of the marrow homotransplant occurred as shown by the appearance of female heterophils in the peripheral circulation. Of this group, 15.5 per cent died early from gastric perforation; in 19 per cent, the marrow transplant was ultimately rejected by the host; 27 per cent died from infection at thirty-three to forty-four days with the marrow transplant intact and still functioning; and 38.2 per cent were alive and well with an intact marrow homotransplant at thirty-two weeks. In 30 per cent the marrow transplant was unsuccessful.

Tetracycline hydrochloride reduced the mortality of the irradiated rabbits from 90 per cent to 75 per cent at thirty-two weeks and addition of bone marrow caused a further reduction to 60 per cent. Fractionation of the total-body irradiation dose reduced postirradiation death from shock.—*Thomas R. Marshall, M.D.*

Brecher, G., Cronkite, E. P., Conard, R. A., and Smith, W. W. Gastric lesions in experimental animals following single exposures to ionizing radiations. *Am. J. Path.*, Jan-Feb., 1958, *34*, 105–120. (From: The National Institute of Arthritis and Metabolic Diseases and National Cancer Institute of the National Institutes of Health, Bethesda, Md.; the Naval Medical Research Institute, Bethesda, Md.; and the Brookhaven National Laboratory, Upton, Long Island, N. Y.)

It has been stated in the past that the gastric mucosa is less sensitive to ionizing radiation than the mucosa of the small intestine. In this series of experiments, dogs, hamsters, and rats were employed and subjected to local and total body irradiation. Cobalt 60 and roentgen therapy units of 200 kvp. (20–25 ma., half-value layer 0.7–0.8 mm. Cu, and focal skin distance 50 cm.) were used as sources of radiation.

There was inhibition of the mitotic activity and death of cells as they entered the next mitosis when both the stomach and small intestine were given radiation. However, the stomach developed epithelial changes more slowly than the small intestine when subjected to a single supralethal exposure. Gastric mucosa underwent changes in the epithelium in about two weeks after exposure. It was also found that regeneration of the epithelium in the stomach arose from the neck of the glands, while in the small intestine, regeneration took place from crypt epithelium.

Frequently it was found that ulcers occurred in the gastric mucosa in the absence of agranulocytosis and hemorrhage, while in the small intestine, late ulcers almost always were associated with pancytopenia and hemorrhage.

Some discussion is given to the use of plasma transfusion, marrow transplants, and antibiotics for the prolongation of life in these experimental animals once they have been subjected to irradiation.—*Earl R. Brown, Jr., M.D.*

Bradshaw, R. Louis, and Setter, Lloyd R. Radioactive particles in the atmosphere at Cincinnati, Ohio. *Pub. Health Rep.*, May, 1958, *73*, 431–438. (From: The Robert A. Taft Sanitary Engineering Center of the Public Health Service, Cincinnati, Ohio.)

Air samples collected by 20 to 30 municipalities in the National Air Sampling network have shown a thousandfold increase in beta radioactivity immediately following tests of nuclear weapons.

The authors had suspected that large amounts of the total radioactivity might be associated with discrete particles which could find their way into the respiratory tract of man. Their paper deals with measurements of the radioactivity in atmospheric particles.

They used a cyclone separator to divide the particles into primary and secondary fractions. These fractions and their particles were considered equivalents of those particles which would be caught in the upper air passages and those which would actually penetrate to the alveoli during normal breathing.

Measurements were made by autoradiographs and gross internal proportional counting. The maximum, minimum and average concentrates of beta activity (30.0, 0.35, and 5.0 micromicrocuries, respectively) are compared with the maximum permissible level of 1,000 micromicrocuries per cubic centimeter of air. The average number of radioactive particles was determined. The activity of particles which could penetrate to the alveoli of the lung was usually less than 5 micromicrocuries and did not exceed 25 micromicrocuries.—*Richard E. Kinzer, M.D.*

BARTON R. YOUNG